1: D45371. Reports Human apM1 mRNA f...[gi:871886] Links

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  AUTHORS   Maeda,K., Okubo,K., Shimomura,I., Funahashi,T., Matsuzawa,Y. and
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  JOURNAL   Biochem. Biophys. Res. Commun. 221 (2), 286-289 (1996)
   PUBMED   8619847
REFERENCE   2  (bases 1 to 4517)
  AUTHORS   Maeda,K.
  JOURNAL   Unpublished
REFERENCE   3  (bases 1 to 4517)
  AUTHORS   Maeda,K.
  TITLE     Direct Submission
  JOURNAL   Submitted (27-JAN-1995) Kazuhisa Maeda, Osaka University, Institut
            for Molecular and Cellular Biology; Yamada-oka 1-3, Suita, Osaka
            565-0871, Japan (E-mail:kmaeda@imed2.med.osaka-u.ac.jp,
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☐ 1: BAA08227. Reports a novel adipose s...[gi:871887]


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ACCESSION   BAA08227
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  JOURNAL   Biochem. Biophys. Res. Commun. 221 (2), 286-289 (1996)
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  AUTHORS   Maeda,K.
  JOURNAL   Unpublished
REFERENCE   3  (residues 1 to 244)
  AUTHORS   Maeda,K.
  TITLE     Direct Submission
  JOURNAL   Submitted (27-JAN-1995) Kazuhisa Maeda, Osaka University, Institut
            for Molecular and Cellular Biology; Yamada-oka 1-3, Suita, Osaka
            565-0871, Japan (E-mail:kmaeda@imed2.med.osaka-u.ac.jp,
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ADIPOCYTE, C1Q, AND COLLAGEN DOMAIN CONTAINING; ACDC

Alternative titles; symbols

ADIPOSE MOST ABUNDANT GENE TRANSCRIPT 1; APM1
GELATIN-BINDING PROTEIN, 28-KD; GBP28
ADIPONECTIN
ACRP30
ADIPOCYTE-SPECIFIC SECRETORY PROTEIN
ADIPONECTIN DEFICIENCY, INCLUDED

Gene map locus 3q27

TEXT

DESCRIPTION

Adiponectin is a hormone secreted by adipocytes that regulates energy homeostasis and glucose and lipid metabolism. Adipocytes also produce and secrete proteins such as leptin (LEP; 164160), adipsin (factor D; 134350), various other complement components (e.g., properdin (see 138470) and C3a (see 120700)), and tumor necrosis factor (TNF; 191160), suggesting a possible link to the immune system. Adiponectin, an adipose tissue-specific plasma protein, has antiinflammatory effects on the cellular components of the vascular wall (10,11:Ouchi et al., 1999, 2000).

CLONING

By constructing and screening an adipose tissue cDNA library for novel genes, Maeda et al. (1996) isolated a cDNA encoding APM1, an adipose tissue-specific collagen-like factor. Sequence analysis predicted that the 244-amino acid secretory protein has a signal peptide but no transmembrane hydrophobic stretch, and a short N-terminal non-collagenous sequence followed by a short collagen-like motif of G-X-Y repeats. APM1 shares significant similarity to collagen X (see 120110), collagen VIII (see 120252), and complement protein C1q (see 120550) within the C terminus. Northern blot analysis detected a 4.5-kb APM1 transcript in adipose tissue but not in muscle, intestine, placenta, uterus, ovary, kidney, liver, lung, brain, or heart.

Saito et al. (1999) cloned an adipose tissue-specific gene they termed GBP28. They stated that the GBP28 protein is encoded by the APM1 mRNA identified by Maeda et al. (1996).

GENE STRUCTURE

By genomic sequence analysis, Saito et al. (1999) and Schaffler et al. (1999) determined that the GBP28 gene spans 16 kb and contains 3 exons, and that the promoter lacks a TATA box. By Southern blot and genomic sequence analyses, Das et al. (2001) determined that the mouse gene, which they termed Acrp30 (adipocyte complement-related protein, 30-kD), contains 3 exons and spans 20 kb.

GENE FUNCTION

By RNase protection and Western blot analysis, Schaffler et al. (1999) showed that APM1 is expressed by differentiated adipocytes as a 33-kD protein that is also detectable in serum. By sequence comparisons, they found links between APM1 and TNF family ligands as well as to cytokines expressed by T cells.

Using cell ELISA analysis, Ouchi et al. (1999) determined that the APM1 gene product, which they termed adiponectin, suppressed TNF-induced monocyte adhesion to aortic endothelial cells (HAECs), as well as expression of vascular cell adhesion molecule-1 (VCAM1; 192225), selectin E (SELE; 131210), and intercellular adhesion molecule-1 (ICAM1; 147840) on HAECs, in a dose-dependent manner. These results indicated that adiponectin may attenuate the inflammatory response associated with atherogenesis. In addition, Ouchi et al. (1999) found that plasma adiponectin values were significantly lower in patients with coronary artery disease compared with those of subjects matched for age and body mass index. By immunoblot analysis, Ouchi et al. (2000) extended these studies to show that adiponectin suppresses TNF-induced I-kappa-B-alpha (IKBA; 164008) phosphorylation and nuclear factor kappa-B (NFKB; see 164011) activation without affecting the interaction of TNF and its receptors or other TNF-mediated phosphorylation signals. The inhibitory effect was accompanied by cAMP accumulation, which could be blocked by adenylate cyclase or protein kinase A (PKA; see 176911) inhibitors. These results, together with a finding by Arita et al. (1999) that plasma adiponectin values are low in obese subjects, suggested that adiponectin levels may be helpful in assessing the risk for coronary artery disease.

Tagami et al (2004) studied adiponectin levels in 31 female patients with anorexia nervosa and in 11 with bulimia nervosa. Serum adiponectin concentrations in anorexia nervosa and bulimia nervosa were significantly lower than those in normal-weight controls. These results were unexpected in light of reports that circulating adiponectin levels are downregulated in obesity (Arita et al., 1999) and that weight reduction increases plasma adiponectin levels (Yang et al., 2001); levels were high in constitutionally thin subjects and low in obese subjects, which provided a negative correlation with body mass index (BMI) and body fat mass. In contrast, serum leptin (164160) levels correlated very well with BMI and fat mass among all the patients and controls. The concentrations of adiponectin after weight recovery increased to the normal level despite a relatively small increase in BMI. The authors suggested that abnormal feeding behavior in patients with eating disorders may reduce circulating adiponectin levels, and that weight recovery can restore it.

Using hematopoietic colony formation assays, Yokota et al. (2000) showed that adiponectin inhibited myelomonocytic progenitor cell proliferation, at least in part due to apoptotic mechanisms, at physiologic concentrations of the protein (approximately 2.0 to 17 micrograms/ml in plasma). Analysis of colony formation from CD34 (142230)-positive stem cells in the presence of a combination of growth factors showed that CFU-GM (myelomonocytic) but not BFU-E (erythrocytic) colony formation was inhibited by adiponectin and by complement factor C1q. Proliferation of lymphoid cell lines was not inhibited by adiponectin. Northern blot analysis revealed that adiponectin-treated cells had reduced expression of the antiapoptotic BCL2 gene (151430) but not of apoptosis-inducing factors such as BAX (600040). Analysis of macrophage function established that adiponectin suppresses phagocytic activity as well as lipopolysaccharide (LPS)-induced TNF, but not interleukin-1B (IL1B; 147720) or interleukin-6 (IL6; 147620), production and expression. Blockade of C1QRP (120577), a C1q receptor on macrophages, abrogated the suppression of phagocytic function but not the inhibition of TNF production or myelomonocytic cell proliferation mediated by adiponectin. Yokota et al. (2000) suggested that adiponectin is an important regulator of hematopoiesis and inflammatory responses that acts through C1QRP and other receptors.

Yamauchi et al. (2002) demonstrated that phosphorylation and activation of the 5-prime-AMP-activated protein kinase (AMPK; see 602739) are stimulated with globular and full-length adiponectin in skeletal muscle and only with full-length adiponectin in the liver. In parallel with its activation of AMPK, adiponectin stimulates phosphorylation of acetyl coenzyme A carboxylase (ACC1; 200350), fatty acid oxidation, glucose uptake and lactate production in myocytes, phosphorylation of ACC and reduction of molecules involved in gluconeogenesis in the liver, and reduction of glucose levels in vivo. Blocking AMPK activation by a dominant-negative mutant inhibits each of these effects, indicating that stimulation of glucose utilization and fatty acid oxidation by adiponectin occurs through activation of AMPK. Yamauchi et al. (2002) concluded that

their data provided a novel paradigm, that an adipocyte-derived antidiabetic hormone, adiponectin, activates AMPK, thereby directly regulating glucose metabolism and insulin sensitivity in vitro and in vivo.

Yokota et al. (2002) found that brown fat in normal human bone marrow contains adiponectin and used marrow-derived preadipocyte lines and long-term cultures to explore potential roles of adiponectin in hematopoiesis. Recombinant adiponectin blocked fat cell formation in long-term bone marrow cultures and inhibited the differentiation of cloned stromal preadipocytes. Adiponectin also caused elevated expression of COX2 (600262) by these stromal cells and induced release of prostaglandin E2. A COX2 inhibitor prevented the inhibitory action of adiponectin on preadipocyte differentiation, suggesting involvement of stromal cell-derived prostanoids. Furthermore, adiponectin failed to block fat cell generation when bone marrow cells were derived from COX2 heterozygous mice. Yokota et al. (2002) concluded that preadipocytes represent direct targets for adiponectin action, establishing a paracrine negative feedback loop for fat regulation. They also linked adiponectin to the COX2-dependent prostaglandins that are critical in this process.

Yang et al. (2001) studied the changes of plasma adiponectin levels with body weight reduction among 22 obese patients who received gastric partition surgery. A 46% increase of mean plasma adiponectin level was accompanied by a 21% reduction in mean body mass index. The authors concluded that body weight reduction increased the plasma levels of a protective adipocytokine, adiponectin. In addition, they inferred that the increase in plasma adiponectin despite the reduction of the only tissue of its own synthesis suggests that the expression of adiponectin is under feedback inhibition in obesity.

Lindsay et al. (2002) found that 70 Pima Indian patients who later developed type II diabetes (see 125853) had, at baseline, lower concentrations of adiponectin than did controls. Those individuals with high concentrations of the protein were less likely to develop type II diabetes than those with low concentrations.

Stefan et al. (2002) measured fasting plasma adiponectin and insulin concentrations and body composition in 30 5-year-old and 53 10-year-old Pima Indian children. Cross-sectionally, plasma adiponectin concentrations were negatively correlated with percentage body fat and fasting plasma insulin concentrations at both 5 and 10 years of age. At age 10 years, percentage body fat ($p = 0.03$), but not fasting plasma insulin, was independently associated with fasting plasma adiponectin concentrations. Longitudinally, plasma adiponectin concentrations decreased with increasing adiposity. Longitudinal analyses indicated that hypoadiponectinemia is a consequence of the development of obesity in childhood.

Williams et al. (2004) determined the extent to which low maternal plasma adiponectin is predictive of gestational diabetes mellitus (GDM), a condition that is biochemically and epidemiologically similar to type II diabetes, using a prospective, nested case-control study design to compare maternal plasma adiponectin concentrations in 41 cases with 70 controls. Adiponectin concentrations were statistically significantly lower in women with GDM than controls (4.4 vs 8.1 microg/ml, P less than 0.001). Approximately 73% of women with GDM, compared with 33% of controls, had adiponectin concentrations less than 6.4 microg/ml. After adjusting for confounding, women with adiponectin concentrations less than 6.4 microg/ml experienced a 4.6-fold increased risk of GDM, as compared with those with higher concentrations (95% confidence interval, 1.8-11.6). The authors concluded that their findings were consistent with other reports suggesting an association between hypoadiponectinemia and risk of type II diabetes.

Biochemical, genetic, and animal studies established a critical role for Acrp30/adiponectin in controlling whole-body metabolism, particularly by enhancing insulin sensitivity in muscle and liver, and by increasing fatty acid oxidation in muscle. Wong et al. (2004) described a widely expressed

and highly conserved family of adiponectin paralogs. They focused particularly on the mouse paralog most similar to adiponectin, CTRP2. At nanomolar concentrations, bacterially produced CTRP2 rapidly induced phosphorylation of AMP-activated protein kinase (see 600497), acetyl-coA carboxylase (see 200350), and mitogen-activated protein kinase (see 176872) in cultured myotubes, which resulted in increased glycogen accumulation and fatty acid oxidation. The authors suggested that the discovery of the family of adiponectin paralogs has implications for understanding the control of energy homeostasis and could provide new targets for pharmacologic intervention in metabolic diseases such as diabetes and obesity.

To study how the biologic activities of adiponectin are transmitted, Hug et al. (2004) performed a series of expression cloning studies to identify cell surface molecules capable of binding adiponectin, using a magnetic-bead panning method that may present higher-valency forms of the adiponectin ligand. Specifically, they transduced a C2C12 myoblast cDNA retroviral expression library into Ba/F3 cells and panned infected cells on recombinant adiponectin linked to magnetic beads. They identified T-cadherin (see 601364) as a receptor for the hexameric and high molecular weight species of adiponectin but not for the trimeric or globular species. Only eukaryotically expressed adiponectin bound to T-cadherin, implying that posttranslational modifications of adiponectin are critical for binding. T-cadherin is expressed in endothelial and smooth muscle cells, where it is positioned to interact with adiponectin. Because T-cadherin is a glycosylphosphatidylinositol-anchored extracellular protein, it may act as a coreceptor for a signaling receptor through which adiponectin transmits metabolic signals.

Sivan et al. (2003) sought to determine if adiponectin is present in human fetal blood, to define its association with fetal birth weight, and to evaluate whether dynamic changes in adiponectin levels occur during the early neonatal period. Cord blood adiponectin levels were extremely high compared with serum levels in children and adults and were positively correlated with fetal birth weights. No significant differences in adiponectin levels were found between female and male neonates. Cord adiponectin levels were significantly higher compared with maternal levels at birth, and no correlation was found between cord and maternal adiponectin levels. The authors concluded that adiponectin in cord blood is derived from fetal and not from placental or maternal tissues.

MAPPING

Using FISH, Saito et al. (1999) mapped the APM1 gene to chromosome 3q27. However, also by FISH, Schaffler et al. (1999) mapped the APM1 gene to 1q21.3-q23. By radiation hybrid analysis, Takahashi et al. (2000) confirmed that the APM1 gene maps to 3q27. Using FISH, Das et al. (2001) mapped the mouse Acrp30 gene to chromosome 16 in a region showing homology of synteny with human 3q27.

MOLECULAR GENETICS

By direct sequencing and restriction fragment polymorphism analysis, Takahashi et al. (2000) identified 2 nucleotide changes in the adiponectin gene in 219 Japanese subjects. A conservative G-to-T substitution at nucleotide 94 of exon 2 was associated with higher but not statistically significant plasma adiponectin values. The allelic frequency of T (71%) was not different between the 142 nonobese and 77 obese subjects. One nonobese individual with coronary artery disease, lung thrombosis, and autoimmune disease had a missense mutation (arg112 to cys; 605441.0001) and a markedly low concentration of plasma adiponectin (1.16 microg/ml).

Vasseur et al. (2002) found 12 single-nucleotide polymorphisms (SNPs) in the APM1 coding region and 5-prime sequences, as well as 4 rare non-synonymous mutations, in exon 3. The 10 most frequent SNPs were genotyped in 1,373 type II diabetes and obese French Caucasian subjects and in all subjects available from 148 type II diabetes multiplex families. A haplotype including 2 5-prime

SNPs was associated with adiponectin levels (P less than 0.0001) and with type II diabetes (p = 0.004). The presence of at least 1 non-synonymous mutation in exon 3 showed evidence of association with adiponectin levels (p = 0.0009) and with type II diabetes (p = 0.005). The authors failed to detect any association with insulin resistance indices. Although family-based association analysis with type II diabetes did not reach significance, results suggested 1) an at-risk haplotype of common variants located in the promoter and 2) rare mutations in exon 3 which may contribute to the variation of adipocyte-secreted adiponectin hormone level, and may be part of the genetic determinants for type II diabetes in the French Caucasian population.

In 253 nondiabetic Italian subjects, Filippi et al. (2004) found that the 276G-T SNP of the adiponectin gene was associated with higher body mass index (BMI) (p less than 0.01), plasma insulin (p less than 0.02), and homeostasis model assessment-estimated insulin resistance (HOMA-IR) (p less than 0.02). When the subjects were divided according to BMI above or below 26.2, subjects in both subgroups carrying the 276G-T SNP had a higher HOMA-IR; however, the difference was highly significant among leaner (p less than 0.001) but not among heavier individuals, indicating that BMI status and the adiponectin gene interact in modulating insulin resistance. In a subgroup of 67 subjects, carriers of the 276G-T SNP had significantly lower (p less than 0.05) mean serum adiponectin levels compared to noncarriers. Filippi et al. (2004) concluded that there is an association between the 276G-T SNP of the adiponectin gene and insulin resistance, and that among leaner individuals, the adiponectin gene appears to determine an increased risk of developing insulin resistance.

OTHER FEATURES

Comuzzie et al. (2001) assayed serum levels of adiponectin in 1,100 adults of predominantly northern European ancestry distributed across 170 families. Quantitative genetic analysis of adiponectin levels detected an additive genetic heritability of 46%. They identified 2 quantitative trait loci influencing adiponectin expression: one on chromosome 5 (606770), and the other on chromosome 14 (606771). The detection of a significant linkage with a quantitative trait locus on chromosome 5 provides strong evidence for a replication of a previously reported quantitative trait locus for obesity-related phenotypes.

ANIMAL MODEL

Maeda et al. (2002) generated mice deficient in adiponectin/ACRP30 by targeted disruption. Homozygous mutant mice showed delayed clearance of free fatty acid in plasma, low levels of fatty acid transport protein-1 (FATP1; 600691) mRNA in muscle, high levels of TNF-alpha (191160) mRNA in adipose tissue, and high plasma TNF-alpha concentrations. The knockout mice exhibited severe diet-induced insulin resistance with reduced insulin-receptor substrate-1 (IRS1; 147545)-associated phosphatidylinositol 3-kinase (PI3K; see 171833) activity in muscle. Viral-mediated adiponectin/ACRP30 expression in knockout mice reversed the reduction of FATP1 mRNA, the increase of adipose TNF-alpha mRNA, and the diet-induced insulin resistance. In cultured myocytes, TNF-alpha decreased FATP1 mRNA, IRS1-associated PI3K activity, and glucose uptake, whereas adiponectin increased these parameters. Maeda et al. (2002) concluded that adiponectin/ACRP30 deficiency and high TNFA-alpha levels in knockout mice reduced muscle FATP1 mRNA and IRS1-mediated insulin signaling, resulting in severe diet-induced insulin resistance.

Yamauchi et al. (2003) crossed mice carrying a transgene for the globular domain of adiponectin with leptin-deficient ob/ob mice or with apoE (107741)-deficient mice. Ob/ob mice carrying the transgene showed reduced insulin resistance, beta-cell degranulation, and diabetes. Amelioration of diabetes and insulin resistance was associated with increased expression of molecules involved in fatty acid oxidation, such as acyl-CoA oxidase (264470), and molecules involved in energy dissipation, such as uncoupling protein-2 (601693) and -3 (602044). When expressed on the ApoE-

deficient background, the globular domain of adiponectin showed reduced atherosclerosis, even though plasma glucose and lipid levels remained the same. The protection from atherosclerosis was associated with decreased expression of class A scavenger receptor (see 153622) and TNFA.

Matsuda et al. (2002) found that adiponectin-deficient mice showed severe neointimal thickening and increased proliferation of vascular smooth muscle cells in a mechanical injury model of restenotic change following balloon angioplasty. Adenovirus-mediated supplement of adiponectin attenuated neointimal proliferation. In cultured smooth muscle cells, adiponectin attenuated DNA synthesis induced by platelet-derived growth factor (PDGFB; 190040), heparin-binding EGF-like growth factor (HBEGF; 126150), and basic fibroblast growth factor (FGF2; 134920). Adiponectin supplementation also attenuated the smooth muscle cell proliferation and migration induced by HBEGF. In cultured endothelial cells, adiponectin attenuated HBEGF expression stimulated by TNF-alpha. Matsuda et al. (2002) concluded that a therapeutic strategy to increase plasma adiponectin should be useful in preventing vascular restenosis after angioplasty.

Qi et al. (2004) demonstrated that adiponectin acts in the brain to decrease body weight. They detected a rise in adiponectin in cerebrospinal fluid after intravenous injection, consistent with brain transport. In contrast to leptin (164160), intracerebroventricular administration of adiponectin decreased body weight mainly by stimulating energy expenditure. Full-length adiponectin, mutant adiponectin with cysteine-39 replaced with serine, and globular adiponectin were effective, whereas the collagenous tail fragment was not. Lep(ob/ob) mice were especially sensitive to intracerebroventricular injection and systemic adiponectin, which resulted in increased thermogenesis, weight loss, and reduction in serum glucose and lipid levels. Adiponectin also potentiated the effect of leptin on thermogenesis and lipid levels. While both hormones increased expression of hypothalamic corticotropin-releasing hormone (CRH; 122560), adiponectin had no substantial effect on other neuropeptide targets of leptin. Agouti mice (see 600201) did not respond to adiponectin or leptin, indicating the melanocortin pathway may be a common target.

Shklyaev et al. (2003) generated a series of recombinant adeno-associated virus vectors of serotypes 1 and 5 encoding mouse Acrp30 cDNAs. The long-term expression of recombinant vectors was tested after intramuscular or intraportal injection in female Sprague-Dawley rats with diet-induced obesity. A single peripheral injection of 10(12) physical particles of Acrp30-encoding vectors resulted in sustained (up to 280 days) significant reduction in body weight, concomitant with the reduction in daily food intake. Acrp30 treatment resulted in a higher peripheral insulin sensitivity measured by the intraperitoneal glucose tolerance test in fasted animals. Ectopic expression of the Acrp30 transgene resulted in modulation of hepatic gluconeogenesis and lipogenesis as demonstrated by the reduction in the hepatic expression of 2 key genes: PEPCK (261680) and SREBP1C (184756). Shklyaev et al. (2003) concluded that these data showed successful peripheral therapy in a clinically relevant model of human obesity and insulin resistance.

ALLELIC VARIANTS
(selected examples)

.0001 ADIPONECTIN DEFICIENCY [ACDC, ARG112CYS]

In a nonobese individual with coronary artery disease, lung thrombosis, and autoimmune disease, Takahashi et al. (2000) identified a C-to-T transition at nucleotide 383 in exon 3 of the APM1 gene, resulting in an arg112-to-cys substitution. This individual had a markedly low concentration of plasma adiponectin (1.16 microg/ml).

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Blood 96: 1723-1732, 2000.
PubMed ID : 10961870

GeneCard for protein-coding ADIPOQ GC03P188044

adiponectin, C1Q and collagen domain containing

Symbol approved by the HUGO Gene Nomenclature Committee (HGNC) database

Services Databases Literature Disorders SNPs Paralogs Orthology Expression Transcripts Drugs Compounds Ontologies Pathways Families Proteins Genomic Location Aliases

Aliases and Descriptions (According to [1]HGNC, [2]Entrez Gene, [3]UniProt/Swiss-Prot, [4]UniProt/TrEMBL, [5]GDB, [6]OMIM, and/or [7]GeneLoc)

About Top

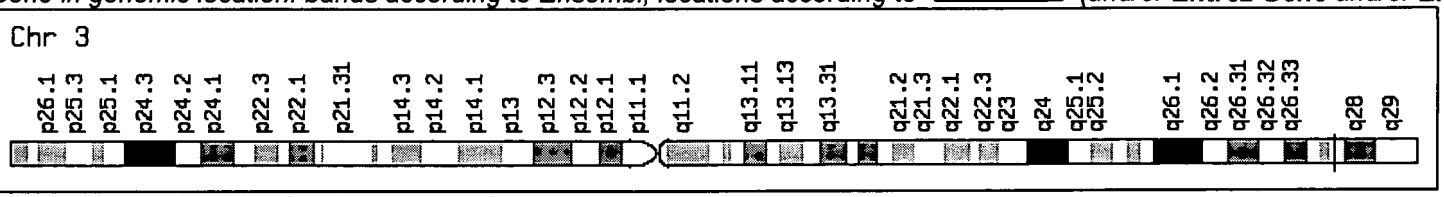
- ACDC [2]
- ACRP30 [2]
- APM-1 [2]
- APM1 [2]
- AdipoQ
- GBP28 [2]
- adiponectin
- adiponectin, C1Q and collagen domain containing [1, 2]
- Adiponectin precursor (Adipocyte, C1q and collagen domain containing protein) (30 kDa adipocyte complement-related protein) (ACRP30) (Adipose most abundant gene transcript 1) (apM-1) (Gelatin-binding protein). [3]

Genomic Location (According to GeneLoc and/or HGNC, and/or Entrez Gene (NCBI build 35), Genomic Views According to UCSC and Ensembl)

About Top

Chromosome: **3**
Entrez Gene cytogenetic band: **3q27** *Ensembl cytogenetic band:* **3q27.3**

Gene in genomic location: bands according to Ensembl, locations according to GeneLoc *(and/or* ***Entrez Gene*** *and/or* ***Ensembl*** *if different)*



GeneLoc gene densities for chromosome 3

GeneLoc location for GC03P188044: *(about GC identifiers)*

Start:	**188,043,165** bp from *pter*
End:	**188,058,954** bp from *pter*
Size:	**15,789** bases
Orientation:	**plus** strand

	Genomic View: UCSC Golden Path with GeneCards custom track
Proteins (According to UniProt, and/or Ensembl, and/or MIPS PEDANT, RefSeq according to NCBI, PDB rendering according to OCA) ***About Top***	**UniProt/Swiss-Prot:** ADIPO_HUMAN, Q15848 • **Size**: 244 amino acids; 26414 Da • **Subunit**: Homooligomer (Potential). • **Subcellular location**: Secreted. • **Pharmaceutical**: Adiponectin might be used in the treatment of diabetes type 2 and insulin resistance. **REFSEQ proteins:** NP_004788.1 **ENSEMBL proteins:** ENSP00000320709
Protein Domains/ Families (According to InterPro, ProtoNet, UniProt, and/or BLOCKS) ***About Top***	**InterPro Domains and Families:** IPR008983 TNF_like IPR008161 Clg_helix IPR008160 Collagen IPR001073 C1q Graphical View of Domain Structure for UniProt Entry Q15848 **ProtoNet protein and cluster:** Q15848 **Blocks protein families:** IPB001073 Complement C1q protein IPB008160 Collagen triple helix repeat IPB008161 Collagen helix repeat **UniProt/Swiss-Prot:** ADIPO_HUMAN, Q15848 • **Function**: Important negative regulator in hematopoiesis and immune systems; may be involved in ending inflammatory responses through its inhibitory functions. Inhibits endothelial NF-kappa-B signaling through a cAMP-dependent pathway. Inhibits TNF-alpha- induced expression of endothelial adhesion molecules. Involved in the control of fat metabolism and insulin sensitivity. • **Similarity**: Contains 1 C1q domain. • **Similarity**: Contains 1 collagenous domain.
Ontologies and Pathways (According to Gene Ontology Consortium 2005-04-04, and KEGG) ***About Top***	**5 Gene Ontology (GO) terms (links to tree view) are shown for ADIPOQ:** GO:0005179 hormone activity GO:0005576 extracellular region GO:0005737 cytoplasm GO:0006091 generation of precursor metabolites and energy GO:0006817 phosphate transport
Drugs & Compounds	

(Chemical Compounds according to bioalma and Drugs according to PharmGKB)

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About Top

Transcripts (GenBank/EMBL/DDBJ Accessions According to Unigene (Build 183 Homo sapiens; Apr 17 2005) or GenBank, RefSeq According to Entrez Gene, Assembly According to MIPS, DOTS (version 9), and/or AceView, protein sequences according to UniProt, ESTs according to GeneTide, alternative splicing isoforms according to ASD, Expression Assays from Applied Biosystems)

REFSEQ mRNAs: *(Click AB for Applied Biosystems TaqMan ® Gene Expression Assays)*

AB NM_004797.2

Gene/cDNA:

AJ131463.1 NT_005612.14 AJ131461.1 AJ131460.1 NC_000003.9 AJ131459.1 AJ131462.1 NT_086644.1 AB012165.2

24/45 AceView cDNA sequences are shown. Click here to see all of them:

AU121917 BQ889392 BX282473 CB265535 CB265759 CB266525 CD514622 CD515608 CD516758 NM_004797 AA321105 AA339798 AL832470 AU147646 AX767959 BQ717765 BQ876848 CB270806 CB999000 CD000104 CD104471 CD244690 CD516223 D45371

UniProt/Swiss-Prot protein sequence: ADIPO_HUMAN, Q15848

About Top

ADIPOQ expression in normal human tissues

AB Applied Biosystems TaqMan ® Gene Expression Assays for ADIPOQ

Expression according to [1] GeneNote / [2] GeneAnnot / GeneTide

5 probe-sets matching ADIPOQ are shown (see all 5)

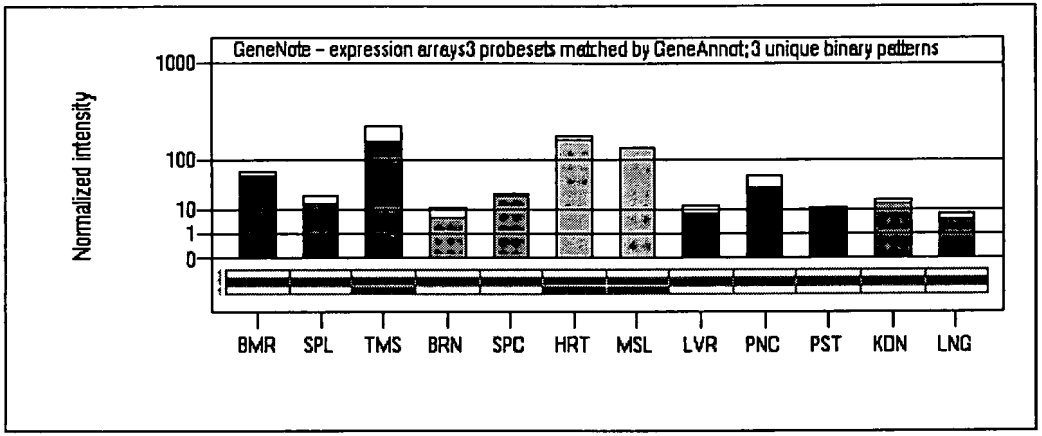
Affymetrix probe-set	Array	GeneAnnot data			GeneNote data		GeneTide data				
		# genes	Sensitivity	Specificity	Correlation	Length	Gb_Accession	Consensus	Uniqueness	Score	Rank
207175_at[2]	U133Plus2	1	1.00	1.00	--	--	--	--	--	--	--
207175_at[2]	U133-A	1	1.00	1.00	--	--	--	--	--	--	--
40658_r_at[2]	U95-A	1	1.00	1.00	0.98	0.57	--	--	--	--	--
40657_r_at[2]	U95-A	2	1.00	0.94	0.99	0.77	--	--	--	--	--
69842_f_at[2]	U95-D	445	0.38	0.01	0.13	1.98	--	--	--	--	--

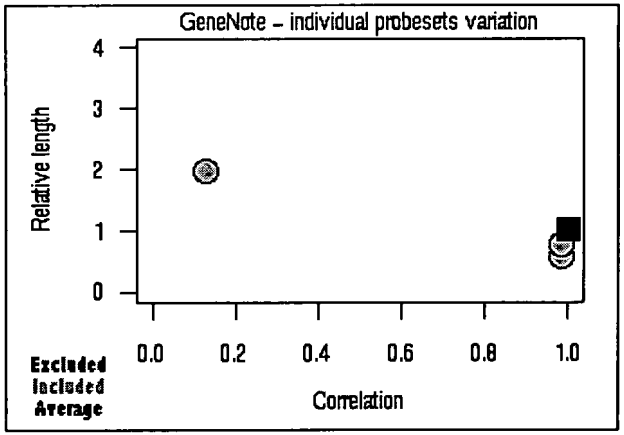
About this table

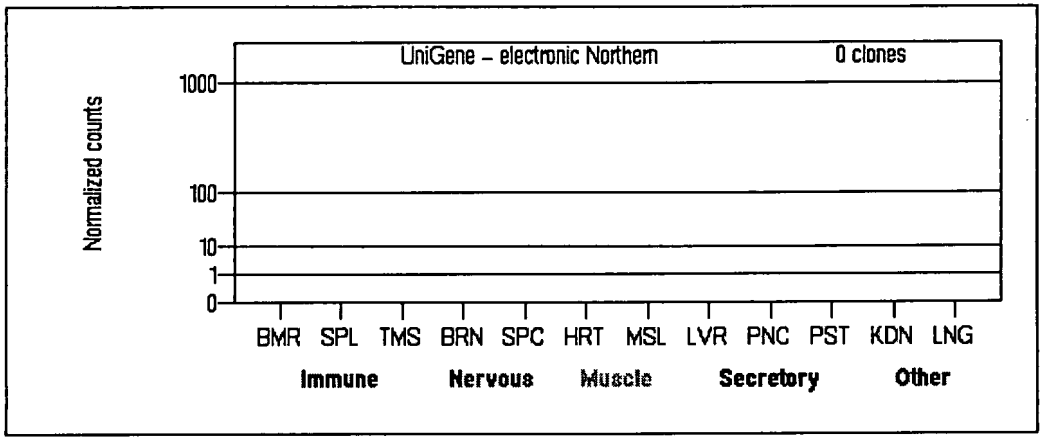
Expression in Human Tissues
(Experimental results according to [1]GeneNote,

probe sets-to-genes annotations according to [2]GeneAnnot, [3]GeneTide, Electronic Northern calculations according to data from UniGene (Build 183 Homo sapiens), SAGE tags according to CGAP, plus additional links to SOURCE, and/or UniProt, Expression Assays from Applied Biosystems)

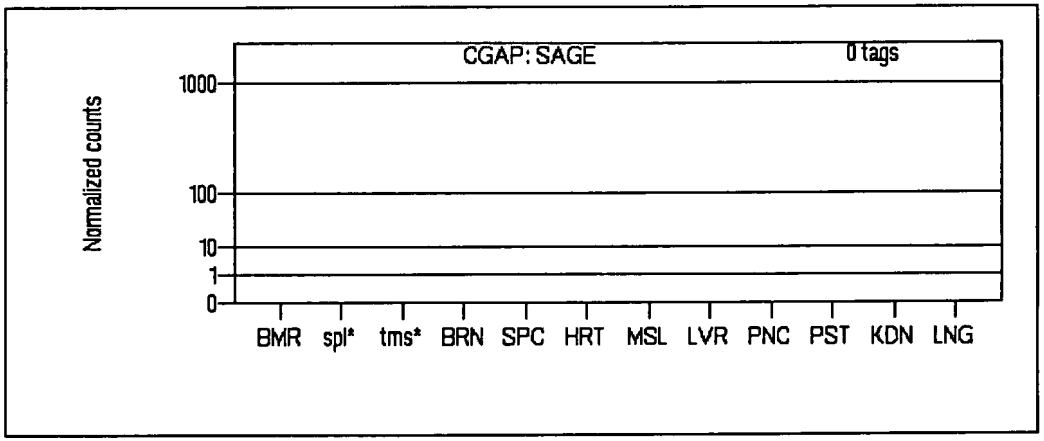
About *Top*







Tissue		Clones per gene	Total clones
BMR	Bone marrow	0	17,515
SPL	Spleen	0	13,074
TMS	Thymus	0	9,104
BRN	Brain	0	183,583
SPC	Spinal cord	0	588
HRT	Heart	0	14,037
MSL	Skeletal muscle	0	69,632
LVR	Liver	0	50,273
PNC	Pancreas	0	65,918
PST	Prostate	0	63,256
KDN	Kidney	0	75,979
LNG	Lung	0	70,872



Tissue		Tags per gene	Total tags
BMR	Bone marrow	0	36,577
spl*	Spleen	0	0
tms*	Thymus	0	0
BRN	Brain	0	427,603
SPC	Spinal cord	0	54,785
HRT	Heart	0	83,063
MSL	Skeletal muscle	0	107,836
LVR	Liver	0	66,308
PNC	Pancreas	0	43,040
PST	Prostate	0	123,335
KDN	Kidney	0	40,993
LNG	Lung	0	88,708

CGAP SAGE TAG: --

UniProt/Swiss-Prot: ADIPO_HUMAN, Q15848

- **Tissue specificity**: Synthesized exclusively by adipocytes and secreted into plasma.

Similar Genes in Other Organisms
(According to [1]HomoloGene, [2]euGenes, [3]SGD and/or [4]MGD Apr 30 2005, with possible further links to Flybase and/or WormBase)

About *Top*

Orthologs from 5 species are shown

Organism	Gene	Locus	Description	Human Similarity	NCBI accessions
dog (Canis familiari)	ACDC[1]	--	adipocyte, C1Q and collagen domain containing	87.84*(n)* 85.25*(a)*	403625 XM_535838.1 XP_535838.1
chimpanzee (Pan troglodytes)	LOC471032[1]	--	similar to Adiponectin precursor (Adipocyte, C1q and collagen domain containing protein) (30 kDa adipocyte more	99.59*(n)* 99.18*(a)*	471032 XM_526416.1 XP_526416.1
rat (Rattus norvegicus)	Acrp30[1]	--	adipocyte complement related protein of 30 kDa	80.05*(n)* 83.2*(a)*	246253 NM_144744.1 NP_653345.1
mouse (Mus musculus)	Adipoq[4] Acdc[1]	16[4]	adiponectin, C1Q and collagen domain containing[4] adipocyte, C1Q and collagen domain containing[1]	79.64*(n)*[1] 83.2*(a)*[1]	11450[1] NM_009605.3[1] NP_033735.2[1] AF304466[4] AK003138[4] AK041214[4] BC028770[4] BE448765[4] U37222[4] U49915[4]
chicken (Gallus gallus)	LOC404536[1]	--	adiponectin	68.25*(n)* 71*(a)*	404536 NM_206991.1 NP_996874.1

About this table

No similarity-to-human data found for ADIPOQ in HomoloGene for: *Sus scrofa, Bos taurus, Danio rerio, Drosophila melanogaster, Caenorhabditis elegans, Saccharomyces cerevisiae, Xenopus laevis, Silurana tropicalis, Oncorhynchus mykiss, Anopheles gambiae, Arabidopsis thaliana, Chlamydomonas reinhardtii, Glycine max, Hordeum vulgare, Lycopersicon esculentum, Magnaporthe grisea, Oryza sativa, Saccharum officinarum, Pinus taeda, Zea mays, Triticum aestivum, Vitis vinifera, Neurospora crassa, Schizosaccharomyces pombe, Ciona intestinalis, Dictyostelium discoideum, Eremothecium gossypii, Kluyveromyces lactis, Medicago truncatula, Plasmodium falciparum, Schistosoma mansoni, Sorghum bicolor, Toxoplasma gondii*

Paralogs
(Paralogs according to [1]HomoloGene and [2]Ensembl, Pseudogenes according to [3]pseudogene.org)

About *Top*

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10 NCBI SNPs are shown (see all 74)
(Click AB for Applied Biosystems TaqMan ® Genotyping Assay) (see all 23)

AB	Genomic Data				Transcription Data				Allele Frequencies				
	SNP ID	Valid	Chr 3 pos	Sequence	Recs	AA Chg	Type	More	Recs	Minor allele	Pop	Total sample	More
--	rs17366743	F	188054791(+)	TGCCTATGTAC/TACCGCTCAGC	1	Y/H	ns		0	--	--	--	--

SNPs/Variants (According to the NCBI SNP Database and UniProt, Genotyping Reagents from Applied Biosystems)

About Top

AB	rs2241766	F,C	188053594(+)	CTCTGCCCGGG/TCATGACCAGG	1	G/G	syn		1	G:0.27	--	1492	
--	rs9877202	F,C,A	188052309(+)	AGAGTGCAATA/GATAGAGCTAA	1	--	utr		0	--	--	--	--
AB	rs822394	F,C,A	188049430(+)	TGTGCTAATCA/CCACTCTTGTA	1	--	utr		1	A:0.40	--	184	
AB	rs2082940	F,C,A	188056866(+)	AGTTTTAAATC/TCTGAACAATT	1	--	utr		0	--	--	--	--
AB	rs1063537	F,C,A	188056777(+)	CAGTGATGTTC/TTTCAAAGATT	1	--	utr		0	--	--	--	--
--	rs1063538	F,C,A	188056885(+)	TTCTCTCTTAC/TATGTGTATTG	1	--	utr		0	--	--	--	--
AB	rs1063539	F,C,A	188058094(+)	GGCACAGAGAC/GAGTCAACTGA	1	--	utr		0	--	--	--	--
AB	rs822395	F,C,A	188049509(+)	GTGGAGAAATA/CTGTCCATAAT	1	--	utr		0	--	--	--	--
--	rs12495941	C,A	188050882(+)	ggtagttaagG/Ttatgcccttt	1	--	utr		0	--	--	--	--

About this table

All NCBI SNPs in ADIPOQ

Disorders & Mutations (in which this Gene is Involved, According to OMIM, UniProt, Genatlas, GeneTests, HGMD, GAD, GDPInfo, BCGD, and/or TGDB.)

About Top

OMIM: 605441
UniProt/Swiss-Prot: ADIPO_HUMAN, Q15848

- **Disease**: defects in adipoq are the cause of adiponectin deficiency [mim:605441]. The result is a very low concentration of plasma adiponectin. Decreased adiponectin plasma levels are associated with obesity insulin resistance, and diabetes type 2.

Medical News (Possibly Related Articles in Doctor's Guide)

About Top

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Research Articles (in PubMed. Associations of this gene to articles via bioalma, HGNC, Entrez Gene, UniProt, and/or GAD)

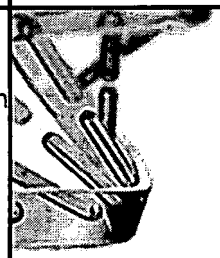
10 articles from PubMed are shown (see all 136):

the following papers are cited by 2 GeneCards sources:

- Genetic variation in the gene encoding adiponectin is associated with an increased risk of type 2 diabetes in the Japanese population. *(2002)*
- The human apM-1, an adipocyte-specific gene linked to the family of TNF's and to genes expressed in activated T cells, is mapped to chromosome 1q21.3-q23, a susceptibility locus identified for familial combined hyperlipidemia (FCH). *(1999)*
- Organization of the gene for gelatin-binding protein (GBP28). *(1999)*
- cDNA cloning and expression of a novel adipose specific collagen-like factor, apM1 (AdiPose Most abundant Gene transcript 1). *(1996)*
- A novel serum protein similar to C1q, produced exclusively in adipocytes. *(1995)*

the following papers are cited by 1 GeneCards source:

- Generation of globular fragment of adiponectin by leukocyte elastase secretedby monocytic cell line THP-1. *(2005)*
- Serum adiponectin concentrations in newborn infants in early postnatal life. *(2004)*

About Top	• Adiponectin may play a part in the pathogenesis of diabetic retinopathy. *(2004)* • Reduced gene expression of adiponectin in fat tissuefrom patients with end-stagerenal disease. *(2004)* • Single nucleotide polymorphisms in the proximal promoter region of the adiponectin(APM1) gene are associated with type 2 diabetes in Swedish caucasians. *(2004)* Search PubMed for ADIPOQ to find abstracts of **research articles** containing this gene name
ADIPOQ in Other Genome Wide Resources: (According to Entrez Gene, HGNC, AceView, euGenes, Ensembl, ECgene, and/or GeneLynx) ***About Top***	Entrez Gene: 9370 HGNC: 13633 AceView: ACDC Ensembl:ENSG00000181092 euGenes: HUgn9370 ECgene: ADIPOQ
ADIPOQ in General Databases, Limited Scope (According to HUGE) ***About Top***	–
ADIPOQ in Specialized Databases (According to ATLAS, Genatlas, HORDE, IMGT, MTDB, LEIDEN and/or UniProt) ***About Top***	–
Services (Reagents available from Applied Biosystems, Clones available from RZPD) ***About Top***	 Applied Biosystems **Products for ADIPOQ:** › TaqMan ® Gene Expression Assays › Free SNP selection tool › TaqMan ® Genotyping Assays Search RZPD for clones of ADIPOQ Clone collection at the German Human Genome Project, Resource Center

Aliases Genomic Location Proteins Families Ontologies Pathways Drugs Compounds Transcripts Expression Orthology Paralogs SNPs Disorders Literature Databases Services

GeneCards **Homepage** - How to **Search** or **Cite** this Database - Last **Update**: 10 May 2005

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Back to top

Obesity, Hypertension, and Insulin Resistance

ZACHARY T. BLOOMGARDEN, MD

This article summarizes material presented at the meeting of the American Society of Hypertension (ASH) in New York, New York, May, 2002, as well as presentations at the American Diabetes Association (ADA) Annual Meeting in San Francisco, California, June, 2002.

At a symposium addressing the relationships between obesity, hypertension, and cardiovascular disease at the ASH, Roger Unger (Dallas, TX) discussed lipotoxicity and the metabolic syndrome. He pointed out that over that past 50 years there has been a great change in the food environment, so that the "mechanism for preloading calories, storing them for when a famine occurred," has led to "hypertrophy and hyperplasia of those adipocytes [. . .]. Famines were eliminated and replaced by a never-ending stream of high-quantity, high-fat, high-carbohydrate foods at the same time that physical exertion dropped to an all-time low." This has led to a progressive increase in obesity, particularly over the past two decades. "As long as the excess fat remains in the adipocyte," he stated, "health is not deleteriously affected," but an "increase in ectopic deposition of lipids" causes the insulin-resistant state, with insulin resistance per se characterized by Unger as "not the proximal cause of the syndrome." Unger examined monogenic disorders of lack of leptin action to understand "the mechanism of the disorder." These syndromes, which lead to components of the metabolic syndrome, suggest that leptin resistance or deficiency may be a more central cause than insulin resistance.

The normal actions of leptin can be seen in animal models of obesity, with overfeeding leading to hyperleptinemia, which may cause fat to deposit primarily in the adipocyte. Normal islets, as an example, "fill up with triglycerides" when incubated with fatty acids, but this can be prevented by administration of leptin. When leptin action is insufficient, as seen in the fatty/fatty (*fa/fa*) rat with loss-of-function mutation of the leptin receptor or the leptin-deficient *ob/ob* rat, there is a marked increase in tissue fat. *fa/fa* rats show both heart and muscle "loaded with triglyceride," suggesting that "leptin increases tolerance for fat just as insulin increases tolerance for glucose."

Obesity in the *fa/fa* animal leads to an increase in cardiac output to maintain the needs of excess body tissue. Cardiac function deteriorates, with initial cardiac hypertrophy leading to a pattern resembling that seen in dilated cardiomyopathy. Increased cardiomyocyte apoptosis, as shown by DNA laddering, can be seen in this setting. Levels of the sphingomyelin derivative ceramide increase with obesity and may mediate these effects, and blockers of serine palmityl transferase (which condenses palmityl CoA with serine to form ceramide) can prevent this process. Ceramide precursors lead to more rapid ceramide synthesis and increase insulin resistance in these animal obesity models. In the islets, after diabetes has occurred in these models, extensive mitochondrial damage is seen in β-cell remnants, a process prevented by troglitazone administration. High levels of fatty acids suppress anti-apoptotic processes, while a transgenic *fa/fa* model overexpressing leptin receptors in the islets is protected from this fat-induced apoptosis.

Aspects of these processes appear to occur in human obesity. Tissue triglyceride may be synthesized from glucose as well as from circulating free fatty acids (FFAs), or may derive from VLDL triglyceride, suggesting multiple potential sources of lipotoxicity. Myocyte fat levels, measured using magnetic resonance scanning, show correlation with the degree of adiposity and obesity may be associated with increased myocardial fat in humans. Unger suggested that the condition of "fatty heart," originally noted by William Harvey and subsequently studied by early cardiologists, should be more of a concern.

Gerard Ailhaud (Nice, France) discussed the differing metabolic characteristics of visceral and subcutaneous (SC) fat. Adipose tissue plays a role in energy regulation and can be considered a secretory organ supplying energy needs during exercise via FFAs. "The problem is the management of levels" of FFAs. In vitro studies suggest that the smaller visceral adipocytes undergo more lipolysis, with more β-adrenergic receptors leading to greater activity of hormone-sensitive lipase, while insulin has a stronger antilipolytic effect on the larger SC adipocytes, which have greater α-2 adrenergic receptor levels. Thus, the α-2 adrenergic response leads to accumulation of fat, but in a fashion of potential benefit in terms of sequestration of fatty acids in the adipocyte, with similarity to the effects of thiazolidinedione administration. Local production of cortisol may be greater in visceral fat, while tumor necrosis factor (TNF)-α and leptin are produced to a greater extent in SC fat. Exercise promotes mobilization of lipid from SC adipocyte tissue in nonobese individuals, but this process is decreased in obesity and can be restored by administration of the α-2 adrenoreceptor antagonist phentolamine.

Zachary T. Bloomgarden, MD, is a practicing endocrinologist in New York, New York, and is affiliated with the Diabetes Center, Mount Sinai School of Medicine, New York, New York.

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ADA, American diabetes Association; ADMA, asymmetric dimethyl arginine; ARB, angiotensin receptor blocker; ASH, American Society of Hypertension; ATP, Adult Treatment Panel; BAT, brown adipose tissue; BP, blood pressure; CHD, coronary heart disease; CHF, congestive heart failure; CVD, cardiovascular disease; ESRD, end-stage renal disease; FA, free fatty acid; HOT, Hypertension Optimal Treatment; IDL, intermediate density lipoprotein; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IRS, insulin resistance syndrome; LCAT, lecithin-cholesterol acyl transferase; LPL, lipoprotein lipase; NASH, nonalcoholic steatohepatitis; NHANES, National Health and Nutrition Examination Survey; PCOS, polycystic ovary syndrome; RGZ, rosiglitazone; SC, subcutaneous; SNS, sympathetic nervous system; SSPG, steady-state plasma glucose; TNF, tumor necrosis factor; UKPDS, U.K. Prospective Diabetes Study; WHO, World Health Organization.

Three research presentations at this symposium addressed further aspects of the interrelationship between obesity and hypertension. Weiguo Zhang et al. (Dallas, TX), noting that leptin might in principle either increase blood pressure (BP) by causing sympathetic activation or lower BP by renal vascular and metabolic effects, studied rodents with high-fat diet–induced obesity characterized by increased plasma leptin and increased BP and a second group with high-sodium diet–induced hypertension. They reported that with adenoviral leptin gene therapy to increase leptin levels, the BP decreased in both animal models, with reduced food intake and body weight in the high sodium diet animals. Raji et al. (Boston, MA) (also reported in 1453-P) studied the effect of rosiglitazone (RGZ) on BP, noting that potential mechanisms of the association between hypertension and insulin resistance include sympathetic activation, sodium retention, and impaired vasodilation (abstract numbers refer to the abstracts of the 62nd ADA Scientific Sessions, *Diabetes* 51 [Suppl. 2], 2002). Twenty-four normal-to-high renin hypertensive persons who were not receiving angiotensin-converting enzyme inhibitors (ACEIs) received RGZ 4 mg twice daily for 16 weeks. Mean 24-h BP decreased from 138/85 to 134/80 mmHg, the decrease correlating with the improvement in insulin sensitivity. "Non-dippers" whose BP falls <10 mmHg in night versus day had similar BP fall to dipper, and showed restoration of circadian variation. Rahmouni et al. (Iowa City, Iowa) studied the molecular mechanisms of insulin-induced sympathetic excitation, showing that insulin increased sympathetic activity in lumbar sympathetic nerves and brown adipose tissue (BAT). This effect was not altered by the PKC-α inhibitor LY333531, although mitogen-activated protein kinase inhibitors blunted the BAT sympathetic response.

Hypertension and diabetes

At a symposium at the ASH meeting on the pathophysiology of hypertension in diabetes, Luis Ruilope (Madrid, Spain) further discussed the interrelationships among diabetes, obesity, insulin resistance, and hypertension. Ruilope suggested that obesity is the initiating factor and focused on the increasingly accepted importance of the metabolic syndrome. Obesity may affect BP via leptin, which increases sympathetic activity and may mediate increases in catecholamines, or via activation of the renin-angiotensin system. Angiotensin II levels are high in obesity, and the presence of increased glomerular pressures suggests activation of the renin-angiotensin system.

It is crucial, Ruilope stated, that general physicians diagnose the "quintet" of central obesity, hypertension, dyslipidemia (high triglyceride and low HDL), and glucose intolerance characterizing the metabolic syndrome. Based on data from the Third National Health and Nutrition Examination Survey (NHANES) and using the criteria for metabolic syndrome of the Adult Treatment Panel (ATP) III that one have at least three of BP measurements >130/85, fasting glucose ≥110 mg/dl, fasting triglycerides ≥150 mg/dl, HDL <40 mg/dl if male and <50 mg/dl if female, and waist circumference >102 cm if male and >88 cm if female (1), 47,000,000 subjects in the U.S. are affected (2). In Spain, despite "the so-called Mediterranean diet," Ruilope noted that the metabolic syndrome is seen in ~40% of the population over age 60 years. In a survey of 4,057 patients in hypertension and renal clinics in Spain, mean BMI was 29 kg/m^2, <20% had BP <130/80 mmHg, 20% of the patients had diabetes, and 15% had impaired fasting glucose (IFG). In addition, 30% of the subjects had microalbuminuria and an additional 10% had macroalbuminuria; decreased renal function was present in one-third, with the frequencies of diabetes and IFG doubled in this group. Cardiovascular disease (CVD) similarly appears to be associated with insulin resistance, with studies from Sweden showing that one-quarter of patients with myocardial infarction have previously undiagnosed diabetes, and an additional 41% have IGT (3).

Ruilope noted that most guidelines merely suggest that obese individuals with hypertension lose weight, without specifically addressing treatment issues in this group. Given the strong relationships among obesity, hypertension, and diabetes, to improve cardiovascular prognosis it may be important to more fully understand various approaches to BP for these patients. Diuretics may be less efficacious than ACEIs in lowering diastolic BP in obese individuals and may increase glucose levels (4). β-blockers appear to increase body weight, particularly in persons with diabetes, as shown in the U.K. Prospective Diabetes Study (5). α-Blockers may then be particularly suitable for subjects with insulin resistance, although this has not been demonstrated in trials addressing clinical events. (Indeed, there is some evidence of increase in CVD risk with use of this agent [ALLHAT Collaborative Research Group: *JAMA* 283:1967–1975, 2000].)

In a study presented at the ADA meeting, Aguilar-Salinas et al. (882-P) reported a nationwide survey of 1,962 individuals in Mexico tested after a 9- to 12-h fast, with 13.1% of the population having the metabolic syndrome as defined above, comprising 5.5, 10.6, 18.3, 24.8, and 31.4% of those with age in the 20s, 30s, 40s, 50s, and 60s, respectively. Kim et al. (937-P) assessed 1,230 persons in Korea, with the metabolic syndrome present in 18%. Ogihara et al. (951-P), addressing the interaction of genetics with environment, compared 211 diabetic and 203 nondiabetic native Japanese men with 68 diabetic and 150 nondiabetic second-generation Japanese-American men. Native Japanese had lower proportion of total caloric intake due to fat, particularly animal fat, and lower BMI, with lower subcutaneous fat levels than in Japanese-American men based on computerized tomography, but with similar visceral fat. Their fasting insulin levels were lower with similar glucose-stimulated insulin, suggesting less insulin resistance, and the prevalence of hypertension (35.3 vs. 67.9%), atherosclerosis of the lower extremities (5.5 vs. 24.4%), and ischemic heart disease (5.1% vs. 24.4%) were all much lower among native Japanese than among Japanese-Americans, respectively, confirming the impact of the metabolic syndrome. Further illustrating the complexity of these interrelationships, during a 5-year follow-up, Tsai et al. (122-OR) examined the influence of age-related changes in fasting plasma glucose on fat distribution in 216 Japanese-American men without diabetes at enrollment. Fasting glucose showed positive association with intra-abdominal fat, independent of age, while having a negative association with SC fat, particularly in older subjects.

Hirose et al. (926-P) noted newly diagnosed hypertension in 9.5, 15.7, and 20.6% of initially normotensive Japanese men in the lowest, intermediate, and highest tertiles, respectively, of insulin re-

sistance at 7 years of follow-up, with age and BMI being other significant factors in a multivariate analysis. Lorenzo et al. (944-P), however, reported that in a survey of individuals in San Antonio and Mexico City, the evidence for association of hypertension with IGT was equivocal, although there was a doubling of risk of hypertension among those with diabetes compared with those with normal glucose tolerance. Whyte et al. (979-P) presented further analysis of the NHANES data. Compared with subjects meeting none of the ATP III criteria, men with three, four, and five risk factors had 3.7-, 4.2-, and 5.2-fold increases, respectively, in 10-year coronary heart disease (CHD) risk. For women, CHD risks were increased 5.8-, 8.9-, and 11.3-fold, respectively. In a provocative analysis, Wilson et al. (980-P) analyzed 3,374 Framingham offspring with a mean age of 62 years, with 33, 31, 22, 10, 3, and 0.2% of men and 48, 31, 13, 7, 2, and 0.1% of women having zero, one, two, three, four, and five of the ATP III factors, respectively. Those with at least three risk factors (and hence classified as having the metabolic syndrome) had a 2.4-fold increase in risk over persons with no risk factors of coronary or overall CVD and an 11.2-fold increase in risk of diabetes, over subsequent follow-up. They noted, however, that there was a similar increase in risk for those with two or more risk factors, "suggesting the definition of the syndrome might be relaxed to include individuals with only two metabolic abnormalities."

Jon Levine (Nashville, TN) described risk factor evaluation approaches for CVD and diabetes at the ASH symposium, pointing out that there are currently no specific guidelines for therapy of the metabolic syndrome, which affects almost half of the population over the age of 60. The likelihood of developing a CVD event increases with age, with cigarette use, and with diabetes, which increases risk six-fold. Middle-aged persons with diabetes have a CVD rate similar to that in subjects without diabetes, but with have a greater history of myocardial infarction. Therefore, it is recommended that subjects with diabetes be treated as though they had already had a CVD event. Improvement in macrovascular disease prognosis with glycemic control in individuals with diabetes is suggested by the findings of the UKPDS. Levine noted that lipids and glucose appeared to be stronger risk markers for CVD than BP in subjects with diabetes in this study, and recommended intensive lipid treatment for diabetes to first reduce LDL cholesterol, to second increase HDL cholesterol, and to third decrease triglyceride levels. In most of the statin trials, he pointed out that there is greater benefit for persons with than for those without diabetes because, although the relative risk decrease is similar, the absolute risk decreases more because of underlying higher CVD rates. Furthermore, these agents may reduce new-onset diabetes and may therefore be beneficial for persons with the metabolic syndrome.

Systolic BP is a strong predictor of CVD risk, particularly in subjects with diabetes. In the UKPDS, BP treatment decreased both microvascular and macrovascular disease. The higher the BP, the greater the rate of loss of renal function, further suggesting benefit of treatment, with the most aggressive BP targets being applied to individuals with diabetes. In the Hypertension Optimal Treatment (HOT) Trial, as diastolic BP was reduced from 85 to 81 mmHg, events were reduced by 50% (6). Urine albumin is not only a predictor of renal disease but also of CVD, and in the HOPE trial the use of ramipril decreased CVD in parallel with the decrease in albuminuria (7). The target for treatment should be <130/80 mmHg, which will require use of three antihypertensive agents in the majority of persons with diabetes.

Thomas Giles (New Orleans, LA) reviewed clinical trial data focusing on the patient with CVD, diabetes, and hypertension. Potential strategies include aggressive control of glycemia, which he stated reduces complications "pretty much across the board." Blood pressure plays an important role in adverse outcomes. In the diabetes subgroup of the HOT study, in which enrollees were randomized to three groups, achieving diastolic BP of 85.2, 83.1, and 81.1 mmHg was associated with linear decreases in adverse outcomes. In the UKPDS there was a 10/5-mmHg difference in BP between the intensive and usual control group of the BP substudy, with a 50% decrease in congestive heart failure (CHF) (8). Tight BP control decreased stroke 45% while glycemic control decreased this end point only 5%. Similarly, BP treatment decreased retinopathy to a greater extent than that seen with glycemic treatment. In the HOPE study, high-risk subjects had a 22% decrease in the combined CVD and mortality risk with ramipril treatment. Individuals without diabetes showed a decrease in new diabetes onset with this treatment. The HOPE study showed decrease in end points with ramipril treatment to a similar extent in those with and without diabetes. Participants in the HOPE study with diabetes had a decrease in CHF by >20%. Also, the RENAAL study showed a decrease in hospitalization for CHF in persons with diabetes treated with losartan (9), and additional observations with this agent were reported in the LIFE trial, which further showed a 25% lower rate of appearance of new diabetes in nondiabetic subjects receiving losartan than among those treated with the comparator agent atenolol (10). Compared with the β-blocker, in patients with diabetes there was reduction in CVD mortality with losartan (11).

Giles emphasized that β-blockers are of benefit in individuals with diabetes, as shown in the MERIT trial of use of metoprolol in persons with CHF (12). Addressing use of calcium-channel blockers, he remarked that in the FACET trial there was worse outcome with amlodipine than with fosinopril alone, but that the combination of the two led to better outcomes than either alone; thus, that these are reasonable agents when used in combination with directly cardioprotective antihypertensive agents (13). Giles recommended as an overall strategy for the hypertensive subject with diabetes, then, the use of aggressive glycemic control as well as aggressive BP control, with ACEIs "the backbone of therapy" and angiotensin receptor blockers (ARBs) as additional important agents. β-blockers are, he suggested, underutilized and are as useful in individuals with as in those without diabetes. Calcium-channel blockers also play important roles for individuals who require multiple drugs to control BP.

Domenic A. Sica (Richmond, VA) pointed out that end-stage renal disease (ESRD) currently is caused by diabetes in half of cases, a frequency predicted to further increase over coming years. The renin-angiotensin axis can be modified with β-blockers, with ACEIs, or with ARBs. The combination of β-blockers with either of the latter two classes is effective, while it is not certain whether combined treatment with ACEIs and ARBs is effective. (There is however evidence that the latter combination does at least reduce al-

buminuria [Rossing et al.: *Diabetes Care* 25:95–100, 2002].) In persons with diabetic nephropathy, BP lowering substantially reduces the rate of decline in renal function. With urine albumin excretion rates of 30–300 mg/day, there is profound endothelial dysfunction at other sites in the body as well. Left ventricular hypertrophy showed strong concordance with microalbuminuria in the LIFE study, further evidence of this relationship. Microalbuminuria progresses to macroalbuminuria without treatment, suggesting the benefit of aggressive treatment. ACEIs are currently regarded as being the primary approach to treatment of subjects with type 1 diabetes and nephropathy, although the end points are less definite for this protective effect existing for individuals with type 2 diabetes and nephropathy. More definite "hard end point" studies have been done with the ARBs irbesartan in the IDNT study (14) and with losartan in the RENAAL study. One must realize that the majority of persons in these trials were treated with three antihypertensive agents in addition to the study drug, with diuretics being the first choice and calcium-channel blockers most often the second choice agents in attempts to lower BP levels. Sica noted that the degree of decrease in proteinuria is greater with the ACEI trandolapril than with calcium-channel blocker verapamil, but that the combination of the two in doses lowering BP to the same degree had even greater effect on proteinuria, suggesting benefit with this combination.

A number of studies at the ADA meeting addressed specific pharmacologic agents in the treatment of subjects with diabetes and hypertension. Wang et al. (1463-P) administered omapatrilat, an inhibitor of both enzymes degrading bradykinin, neutral endopeptidase, and angiotensin-converting enzyme, to insulin-resistant rats. Basal glucose production decreased 35% and glucose production showed a 2.7-fold greater suppression by insulin, while no consistent increase in insulin sensitivity was demonstrated with ramipril or losartan. The effects were blocked by administration of the bradykinin-2 receptor antagonist HOE-140, suggesting increased bradykinin action to mediate this effect. Black et al. (12-LB) compared the antihypertensive efficacy of omapatrilat with that of enalapril in daily dosages up to 80 and 40 mg, respectively, in 3,377 patients with diabetes. Of 775 previously untreated patients, systolic BP decreased 21 vs. 16 mmHg, with adjunctive treatment subsequently added in 15 vs. 25% to achieve levels <140/90 mmHg. For 1,823 previously treated patients, systolic BP decreased 10 vs. 5 mmHg, with adjunctive treatment subsequently added in 31 vs. 37%. An important caution for the new agent is that angioedema occurred in 1.3 vs. 0.4% of patients.

Jacob et al. (635-P) showed increase in fasting glucose from 183 to 198 mg/dl and in triglyceride from 221 to 265 mg/dl in 61 hypertensive individuals with diabetes treated with metoprolol. In contrast, the centrally acting anti-adrenergic moxonidine was associated with decrease in fasting glucose from 206 to 186 mg/dl and in triglyceride 222 to 182 mg/dl in 66 patients, with similar degrees of BP control. Viberti et al. (752-P) treated 223 hypertensive persons with diabetes and microalbuminuria with a combination of perindopril 2–8 mg and indapamide 0.625–2.5 mg daily. Albuminuria decreased 42%, significantly more than the 27% decrease in albuminuria in 224 such patients treated with enalapril 10–40 mg daily, suggesting synergistic benefit of the addition of a diuretic to ACEI treatment. Buckalew et al. (152-OR) treated 74 diabetic hypertensive patients with microalbuminuria with the selective aldosterone blocker eplerenone 200 mg daily, showing 62% decrease in albuminuria, in comparison to 45 and 74% decreases in albuminuria in 74 and 67 patients treated with enalapril 40 mg daily and with enalapril 10 mg plus eplerenone 200 mg daily, respectively. Withdrawal for hyperkalemia was necessary in 6, 2, and 14 subjects, respectively, in the three groups. Blood pressure levels were similar, and the decrease in albuminuria was independent of the degree of BP reduction, suggesting direct renoprotective effect of aldosterone blockade.

Management of the metabolic syndrome

Lewis Landsberg (Chicago, IL), introducing a symposium at the ASH on the mechanisms and management of the metabolic syndrome, stated that obesity and hypertension were first noticed to be associated more than 100 years ago, with prospective demonstration in the 1960s in the Framingham Study. Jean Vague in the 1940s observed the association between upper-body obesity and hypertension, with Scandinavian studies over the past two decades showing the quantitative relationship between the waist-to-hip ratio and these abnormalities. Hyperinsulinemia was shown to be a marker of the insulin-resistant state over the past two decades as well, with studies in the 1980s pioneered by studies of Reaven that showed the relationship between hypertension and insulin resistance. Studies beginning at that time showed the relationship among hypertension, insulin resistance, and sympathetic activation and subsequent recognition of a role of leptin in sympathetic activation and of insulin in the association of hypertension with obesity. Over the coming three decades, 40% of the U.S. population is projected to become obese, with the epidemic of obesity affecting the developing world as well. The age-adjusted prevalence of the metabolic syndrome is now ~24% in the adult population and reaches 50–60% over age 50 years.

James Poole of Baylor University (Houston, TX) discussed hypertension and lipid metabolism, pointing out the complexity of their inter-relationship, based on the contributions of the sympathetic nervous system (SNS) and renin-angiotensin system to the development of hypertension in the metabolic syndrome. There are three components to lipid metabolism, exogenous lipid entry, endogenous lipid synthesis, and remnant metabolism. The endogenous pathway produces VLDLs from endogenous precursors while the exogenous pathway uses breakdown products of dietary lipids to produce chylomicrons. Lipoprotein lipase (LPL) acts in the vascular lumen and is activated in the presence of specific particles, leading to production of intermediate-density lipoproteins (IDLs) from VLDLs, which are metabolized by hepatic lipase, leading to HDL production, with HDL levels enhanced by the action of cholesterol ester transport protein. On the exogenous side, chylomicrons are acted upon and reduced in size to more compact lipoproteins, upon which hepatic lipase then acts. The remnant pathway converts IDLs and chylomicron products into discoid particles, which are then acted upon by lecithin-cholesterol acyl transferase (LCAT) to produce HDL3, with LCAT acting on HDL3 to produce HDL2.

Nicotinic acid, fibrates, and statins

play roles in treatment, and, perhaps, alcohol and estrogens could be used to raise HDL cholesterol. Poole suggested a role for inhibition of the SNS at the postsynaptic level of the α-1 adrenoreceptor by prazosin, doxazosin, and related agents, which consistently influence metabolic pathways in a fashion separate from their effect on peripheral vascular resistance. The drugs decrease total and LDL cholesterol and, to a greater extent, triglyceride levels. Actions include upregulation of peripheral LDL receptors, decrease in gut cholesterol absorption, and upregulation of LPL expression, while synthesis and secretion of VLDL decrease. The degree of endothelium-dependent relaxation is also under SNS regulation and improved by α-1 receptor blockade. Such treatment, then, has the potential to decrease systolic, diastolic, and pulse pressure, to increase HDL cholesterol and apolipoprotein A1, to improve hyperinsulinemia, and to decrease LVH and the atherosclerotic process.

Ronald M. Krauss (Berkley, CA) further discussed the atherogenic lipoprotein changes associated with insulin resistance. The primary lipoprotein disturbances involve low HDL and high triglyceride levels, without a consistent effect on LDL cholesterol "the way we measure it in the clinic." The metabolic syndrome can be assessed with factor analysis, which illustrates the strength of the association of dyslipidemia with the metabolic syndrome and its strong association with adiposity and hyperinsulinemia. Glucose intolerance and hypertension in turn have relationships with dyslipidemia with this approach to statistical analysis. The dyslipidemia caused by abnormalities of the lipases described by Poole reflects impaired VLDL clearance, the effects of hepatic lipase on HDL catabolism, and the effects of hypertriglyceridemia on VLDL production. LDL itself is a heterogeneous set of particles, most arising from VLDL catabolism. The intermediate stage of clearance of abnormal VLDLs leads to production of a small LDL particles, with abnormal and increased transport of cholesterol from HDL into these particles contributing to the low HDL cholesterol level. Peak LDL size is inversely correlated with triglyceride levels, with two groups of individuals in the population, those with larger LDL and low triglyceride levels and those with smaller LDL and high triglyceride levels. The latter group of patients has higher postprandial glucose and insulin levels and lower insulin sensitivity, suggesting small LDL size not only to be associated with the dyslipidemia but also with the insulin resistance of the metabolic syndrome.

These are highly atherosclerotic particles, less rapidly cleared by the LDL receptor and more rapidly entering the subendothelial space and undergoing oxidation, with subsequent plaque formation and inflammatory response. Genetic susceptibility accounts for 40–50% of the variation in LDL size, with several candidate genes identified. Other important modifying effects include dietary fat and carbohydrate, obesity, and pharmacologic agents. Niacin appears to have the greatest effect, and fibrates are also useful in reducing levels of small LDL particles, while statins lower levels of all LDL fractions, and all agents that lower triglyceride levels also change the LDL size distribution to include more of the larger particles. In the Quebec Cardiovascular Study, the combination of low HDL and small LDL particle size was particularly associated with development of CVD (15). In the Familial Atherosclerosis Treatment Study (FATS), treatment of CHD with resins, statins, and niacin resulted in angiographic regression, the single most important predictor of which was the increase in LDL particle size, rather than the change in levels of LDL and of HDL (16). This appears to be particularly relevant to the treatment of individuals with the metabolic syndrome. Interestingly, the thiazolidinediones also appear to cause changes in LDL particle distribution with shift from small to large LDL, with effects documented for troglitazone and RGZ. The relationship between treatment of hypertension and lipoproteins in the metabolic syndrome suggests that α-blockers improve and β-blockers worsen this dyslipidemia, with particular effects on levels of remnant particles and the expected association with triglycerides. Krauss suggested that calculation of HDL-to-triglyceride ratios could be used to infer LDL particle size.

Gerold Reaven (Stanford, CA) discussed insulin resistance, hypertension, and CHD. The steady-state plasma glucose (SSPG) concentration during infusion of somatostatin, glucose, and insulin is a measure of insulin resistance, showing 10-fold variability in apparently normal populations. BMI correlates with higher SSPG, but only accounts for ~25% of the variability in insulin action from person to subject, with physical fitness, as measured by maximal aerobic capacity, also contributing approximately one-quarter of the degree of insulin sensitivity. The remaining half of the determination of insulin sensitivity is presumably genetic. Ethnic groups of European ancestry appear to have greater insulin sensitivity than other ethnic groups. Insulin resistance will lead either to type 2 diabetes and subsequent CHD, or, if insulin secretion is maintained, to the development of the metabolic syndrome without diabetes, and, again, to greatly increased risk of CHD. The metabolic syndrome is associated with increased SNS activity and hypertension, with procoagulant effects, with endothelial dysfunction, and with high uric acid, nonalcoholic steatohepatitis, and, perhaps, certain forms of cancer.

Daylong hyperinsulinemia and hypertriglyceridemia are characteristic of individuals with hypertension and of those with CHD. First-degree relatives of persons with hypertension show similar abnormalities. Hypertension is, however, heterogeneous. When comparing subjects with normal and high BP, hyperinsulinemia is seen in approximately half of the latter but in only one-tenth of the former group. There are important differences between individuals with hypertension and insulin resistance versus those who are insulin sensitive with hypertension, as the former group shows evidence of the characteristic dyslipidemia with low HDL and high triglyceride, evidence of glucose intolerance, and a greater prevalence of electrocardiographic abnormalities, which suggests underlying CHD. Those hypertensive persons with normal lipid patterns are less likely to have cardiac disease. Mononuclear cells from subjects with insulin resistance show enhanced endothelial binding, presumably contributing to CHD development. Asymmetric dimethyl arginine (ADMA) is an endogenous inhibitor of nitric oxide synthase that has been closely linked to CHD. Comparing individuals with and without insulin resistance, ADMA levels are higher in the insulin-resistant group, both with normal and with high BP. Reaven also discussed the triglyceride-to-HDL ratio, suggesting this to be as predictive of the degree of insulin sensitivity as is

the fasting insulin level, as well as suggestive of the individual's level of coronary disease risk. Insulin resistance is also associated with greater degree of sodium retention and greater increase in BP on a high-sodium diet.

In a presentation at the ADA meeting, Lawrence et al. (1670-P) presented data using isotope dilution and arterio-venous difference techniques to measure the rate of norepinephrine entry into the general circulation and into blood draining SC abdominal adipose tissue and forearm muscle as indices of systemic and local sympathoneuronal activity in 22 lean and obese volunteers. Systemic SNS activity was greater with obesity, increased further after feeding, and correlated with BP, while adipose tissue SNS activity was almost 50% lower with obesity and, unlike the finding in lean control subjects, did not increase after feeding. They suggested that obesity is associated with local SNS dysfunction despite increased systemic SNS activity, suggesting potential benefit of selective β_3 adrenoceptor agonists for treatment of obesity. Després et al. (1679-P) characterized 907 men and 937 women aged 18–74 years based on BMI tertile, with cutoffs at 23.2 and 26.6 kg/m^2, and based on the 50th percentile of waist circumference (with cutoff at 88 cm for men and 74 cm for women). BP was similar in men in the lowest BMI tertile with higher abdominal girth to that of men in the top BMI tertile; for women, the highest systolic BP was seen in those in the top BMI tertile with higher abdominal girth. There was no association between fasting insulin and BP when controlling for waist, suggesting that rather than assessing body mass per se it is more important to measure waist circumference in gauging the degree of obesity.

Insulin resistance

At a symposium at the ADA meeting on the insulin resistance syndrome (IRS), an alternative term for the "metabolic syndrome," James B. Meigs (Boston, MA) reviewed its definition and studies of its prevalence. The syndrome was first proposed and has continued to be studied by Gerald Reaven, who suggested that risk factors for heart disease and diabetes cooccur and termed the complex "syndrome X" (17). The San Antonio Heart Study showed that risk factors such as low HDL, hypertension, obesity, and hyperinsulinemia proceed the development of diabetes (18). In the Framingham Offspring Study, dyslipidemia, obesity, hyperinsulinemia, hypertension, and perhaps microalbuminuria occurred together with greater-than-chance frequency (19). Factor analysis has been used to suggest that insulin, triglyceride, HDL cholesterol, obesity, and increased waist circumference comprise the "central" components of the syndrome, with high glucose levels linked but existing as a separate factor and with hypertension again as a separate linked factor. Obesity and hyperinsulinemia may be the most crucial aspects of the IRS. The presence of IRS trait clusters predicts both the development of diabetes and CVD mortality. There are sex and ethnic differences in the causes of the IRS. Using the ATP-III factors and the NHANES data set, women more commonly have increased waist circumference, and men more commonly have increased triglyceride levels, with overall prevalence 24 and 23% in men and women, respectively, and levels increasing with age. Caucasians are more likely to have high triglyceride levels, while BP is more often elevated in African-Americans. The prevalence of the IRS is lowest among African-American males and highest among Mexican-American women. Combined analysis of data from the Framingham, NHANES, and San Antonio studies confirms these differences, with 24–28% of Caucasians and 32–38% of Mexican Americans having the IRS. The World Health Organization (WHO) suggests different criteria, proposing that the definition include increased 2-h postload glucose rather than fasting glucose as in ATP-III, increased BMI rather than waist circumference as in ATP-III, increased triglyceride or low HDL, hypertension (with different thresholds than ATP-III), and albuminuria (which is not included in ATP-III) (20). The Botnia study, which uses this definition, reports variation in prevalence from 34–46% in different European populations.

Meigs noted that the syndrome traits do not have equal predictive weights for specific outcomes, so that, for example, fasting blood glucose is more important than BMI, which in turn exceeds HDL cholesterol, with BP of least importance, in predicting diabetes. Meigs suggested a number of uncertainties, asking whether simply counting the number of traits is "good enough" or whether the traits should be weighed or grouped in clusters. If "trait clusters" are required rather than just counting the number of positive findings, the frequency decreases to ~15 and 25% in Caucasians and Mexican-Americans, respectively, an example of the impact of varying the definition on syndrome prevalence. Further questions are whether BMI or waist circumference is better for classifying individuals, whether insulin or urine microalbumin levels should be measured, and whether persons with diagnosed diabetes or diabetes based on glucose tolerance testing should be included. Meigs pointed out that one could "just identify the traits and treat them," rather than treating the syndrome, unless there is some way in which identifying the IRS confers added benefit. He concluded that there is not even agreement as to the name of the syndrome, and "we still don't actually agree" on many important aspects of the condition, but that it is clearly of great importance, as prevalence is likely to increase in the coming years as obesity increases.

Frederick Brancati (Baltimore, MD) discussed "emerging risk factors" for the IRS, noting that from the perspective of primary prevention it "sometimes feels like an inevitable sequence of events" that leads to diabetes and CVD. The Diabetes Prevention Project (DPP) and other studies suggest benefit of interventions, but even with optimal lifestyle modification there remained a 20% 5-year risk in the DPP and Finnish Prevention Study. Brancati recalled that Osler in 1892 discussed a number of risk factors for type 2 diabetes, including heredity, ethnicity, social class, adiposity, sedentary lifestyle, and overindulgence, as well as what one might now term novel risk factors such as "nervous strain" and worry, brain lesions, environment, infections, and liver disturbances. We now consider well-established risk factors to be age, obesity, inactivity, pregnancy, drugs, and endocrine and monogenic syndromes, and emerging risk factors to include genes, the fetal environment, inflammation, dietary macronutrients, and intracellular lipids, as well as newer risk factors including liver disease, mineral intake, stress and depression with hypothalamic-pituitary-adrenal (HPA) axis activation, abnormal lung function with sleep apnea, and endothelial dysfunction.

Based on NHANES data, subjects with hepatitis C show a 3.8-fold increase in diabetes risk (21), although Brancati

pointed out that either hepatitis C could cause diabetes, diabetes could increase risk of hepatitis C, or both could be caused by some underlying factor. The considerably more common illness, nonalcoholic steatohepatitis (NASH), is also associated with insulin resistance (22,23). In NHANES, 29.1% of adults in the U.S. had increased transaminase levels, with 2.3% related to alcohol use and 1.6% to hepatitis C, suggesting that almost one-quarter of adults have NASH, which is strongly associated with diabetes, particularly among women (24). Evidence that this is not due to alcohol intake has been assembled in a number of investigations. "If it's real," Brancati stated, "it could be associated with a very high population-attributable risk." Possible implications are for use of therapeutic agents targeted to the liver and for avoidance of hepatotoxic substances.

Serum magnesium <1.4 mg/dl is associated with doubling of diabetes risk, although it has some ambiguous features given that the mean level is lower in African-Americans than Caucasians, but magnesium is a stronger risk factor in the latter group (25). The mineral zinc may also be a factor, with Marreiro et al. (569-P) in a study presented at the ADA meeting randomizing 56 obese women with normal zinc levels and normal glucose tolerance to placebo or zinc 30 mg daily for 4 weeks, the latter showing a fall in insulin from 29 to 21 μU/ml, which is indicative of improvement in insulin sensitivity. Mineral supplementation may, then, play a role in preventive treatment of diabetes. As suggested by Osler, depression and stress may be factors in diabetes (26), although again the direction of causality is uncertain, with Brancati noting that subclinical hypercortisolemia from depression could cause insulin resistance (27). In the Atherosclerosis Risk in Communities Study, depressive symptoms were associated with increased fasting insulin, BMI, and triglyceride levels, with a 1.52-fold increase in risk of diabetes in the highest quartile of symptoms (28). A therapeutic implication is that depression/stress reduction might be relevant to diabetes prevention, or, perhaps, that anti-depressant treatment could ameliorate subtle abnormalities in the HPA axis.

Abnormal lung function and sleep apnea may be related to diabetes, as 2-h insulin levels show a progressive rise with increased frequency of sleep apnea. There is also an association of decreased forced vital capacity with diabetes, which might be related to cigarette use or to obesity. At the ADA meeting, Resnick et al. (955-P) reported overnight polysomnogram results in 4,882 persons ≥40 years old without history of CVD; of these subjects, 426 had diabetes. Subjects with diabetes had similar REM sleep times (18.9 vs. 20.1%), adjusted for age and BMI, but a twofold higher prevalence of periodic breathing, indicative of a central nervous system disorder and diagnosed if ≥10 consecutive minutes of a crescendo-decrescendo breathing pattern was observed. This suggested alterations in autonomic or metabolic control of ventilatory systems during sleep. It would be of interest to learn whether nondiabetic individuals with the metabolic syndrome in that study also had evidence of sleep abnormality.

Leif Groop (Malmo, Sweden) discussed genetic associations with what he termed the "dysmetabolic" syndrome. The Botnia study, named for the gulf of Botnia, which lies between Sweden and Finland, involves 9,315 persons from 1,389 families from the two countries. Groop noted that insulin sensitivity itself is only mildly hereditable, with monozygotic twins showing correlation with $r = 0.49$, but dizygotic twins only showing $r = 0.1$. Waist circumference, however, is much more strongly inherited. Genetic contributions to insulin resistance have been investigated by analyzing potential candidate genes and by random gene searches of the entire genome to find excess allele sharing in certain regions. A number of genes have been identified. The β-3 adrenergic receptor variant having substitution of tryptophan for arginine in position 64 is associated with the IRS (29,30), as well as with decreased metabolic rate, which might predispose to obesity. There is also a mutation at position 27 of the β-2 adrenergic receptor associated with high FFA levels. An intronic variant of the skeletal muscle glycogen synthase gene is associated with both insulin resistance and increased CVD mortality. (31,32). The mechanism of the association may be of affected subjects having a lesser effect of exercise on muscle metabolism. The proline 12 to alanine variant of the peroxisome proliferator–activated receptor (PPAR)-γ is a protective mutation that may account for 20% of the population risk of diabetes among Caucasians. (33). The variant is associated with a decrease in fat cell production and becomes manifest in individuals consuming a diet high in saturated fats. A mutation of calpain 10 is associated with insulin resistance and elevated FFA levels. Groop noted that calpain 10 mRNA expression is upregulated in individuals without family history of type 2 diabetes, but not in those at risk, and the level of expression in muscle is associated with insulin insensitivity. The winged helix/forkhead transcription factor gene (FOXC2) is another potential protective allele, which is expressed to a greater extent in visceral than in subcutaneous fat (34). Finally, a gene on chromosome 18P11 is linked to type 2 diabetes only in the highest BMI quintile of the population. The melanocortin receptor (which is also the ACTH receptor) is present in that region and may account for the linkage. Other linkages have been found without identification of potential causative genes, including one on chromosome 17 and one on chromosome 9. Thus, Groop concluded, a number of common variants, many of which influence FFA metabolism or impair scavenger factors, increase diabetes susceptibility.

In a study reported at the meeting, Hara et al. (157-OR) reported that allelic variations in the gene for PPAR-γ coactivator-1 were associated with differences in fasting insulin in 537 type 2 diabetic subjects and 417 nondiabetic subjects. Emphasizing the complexity of gene discovery, Yang et al. (1049-P) used DNA microarrays to analyze gene expression of SC adipose tissue and skeletal muscle biopsies specimens from eight insulin-sensitive and eight insulin-resistant persons. Of the thousands of sequences tested, 618 genes/expressed sequence tags were differentially expressed in adipocytes from the two groups, of which 199 upregulated genes could be assigned to known functional pathways, 101 involved in cell proliferation and 30 in cell growth.

Robert S. Schwartz (Denver, CO) discussed the IRS in the elderly, pointing out that aging is "the most important environmental factor" in causing insulin resistance. Body weight tends to increase through age 55 years in cross-sectional studies, but in longitudinal studies, weight actually tends to increase through age 65–70 years. Furthermore, there is a

decrease in lean body mass with age, so "for any given weight old people are fatter than young people." The deposition of fat shifts more to the visceral location in males after puberty and in women at menopause, and, while at all BMI levels individuals with a low waist-to-hip ratio (WHR) have diabetes risk approximately half that of those with normal or high WHR, even those individuals with normal BMI but high WHR have a threefold increase in diabetes rate. Thus, if obesity is more frequent with aging and , particularly, central obesity, one can expect the concomitants of hyperinsulinemia, diabetes, hypertension, dyslipidemia, coronary disease, elevated thrombotic factors, and homocysteine, as well as other features of obesity such as osteoarthritis, sleep apnea, and increased mortality rates. Analysis of NHANES data shows that the prevalence of diabetes increases with age in the U.S. population (35), and even individuals with normal glucose tolerance have higher postload glucose levels with increasing age.

In treatment, lifestyle intervention may be particularly appropriate for older subjects with the IRS, as shown in the DPP, where metformin had considerably less impact in those over age 60 years, while diet and exercise had similar benefit to that seen in younger age-groups. Schwartz also noted that although weight loss may not be as great with a program focused on exercise as with one focused on diet, the decrease in intra-abdominal fat will be similar with both approaches. Another area that may be important for future treatment is the potential for hormonal mediators of the features of the IRS that appear with aging. Schwartz noted that the IRS has many features in common with hypercortisolemic states, leading one to wonder whether this may be a factor. There is also intriguing evidence of relative decrease in growth hormone action with aging, shown by a decline in insulin-like growth factor 1 levels. Certainly, growth hormone deficiency is associated with increased fat mass, decreased muscle mass, and decreased insulin sensitivity. Finally, many features of hypogonadism appear with age, and there is some evidence that low testosterone is present with aging in men, perhaps similarly to the estrogen deficiency following menopause in women.

Michael Goran (Los Angeles, CA) discussed the IRS in children. He pointed out that type 2 diabetes is now an important problem among obese children and adolescents, having increased 10-fold in frequency over the past two decades in the U.S., particularly in minority populations. In a recent clinic-based study, 25 and 21% of obese children and adolescents, respectively, had IGT (36), and Goran described studies of Hispanic children with positive diabetes family history with IGT present in 38%. An important concept is that a healthy β-cell compensates for insulin resistance, but that in adolescents at risk of diabetes—because of underlying β-cell abnormality—the process is accelerated by the sudden decrease in insulin sensitivity occurring with puberty, which amounts to ~30% in normal adolescents (37) and is particularly prominent with obesity (38). Increased skeletal muscle intracellular lipid may play a role in this process (39). Approaches to treatment include metformin, which has been shown of benefit in adolescent girls with the polycystic ovary syndrome (PCOS) (40). There has been virtually no study of whether exercise is of benefit, and it will also be important to understand whether there is recovery of insulin sensitivity following puberty and what role this may play in the improvement of the IRS in affected adolescents.

In a study presented at the ADA meeting, Goran et al. (1439-P) reported African-American and Hispanic adolescents to have 35 and 29% decreases in insulin sensitivity, respectively, compared with Caucasians; these decreases were not explained by having higher visceral fat levels. Goran also found that the Hispanic adolescents had greater hepatic insulin uptake than the African-American group, which may explain the relatively low insulin levels in the former and higher insulin levels in the latter group. Klein et al. (938-P) reported on the prospective NHLBI Growth and Health Study of 2,379 girls aged 9–10 years at onset, showing that African American girls had higher BMI and fasting insulin levels initially, with a relative increase in obesity, compared with Caucasians during the 10 years of follow-up. Controlling for BMI and pubertal status, African-American ethnicity was associated with higher insulin levels, with differences between the groups increasing over time, potentially increasing risk of diabetes and CVD.

In view of the association of low birth weight with diabetes and CVD, Hermann et al. (1218-P) compared 14 men with birth weight below the 10th percentile and 16 matched control subjects with normal birth weight, all of whom were 21 years of age, and showed that glucose uptake during insulin infusion increased 1.5-fold vs. 2.5-fold, which is suggestive of insulin resistance, albeit forearm endothelial function and vascular reactivity to insulin were comparable. Jeffery et al. (1441-P), Kirkby et al. (1446-P), and Mallam et al. (1449-P) described results of the EarlyBird study of 307 5-year-old children and their parents. Only 1.4% of term infants had birth weight <2.5 kg, and there was no significant relationship between birth weight and insulin resistance, while current weight did show modest correlation with insulin sensitivity. Little correlation was noted between paternal and child insulin sensitivity. Resting energy expenditure measured by indirect calorimetry did not correlate with insulin sensitivity and showed positive correlation with body weight. Interestingly, girls had 27% more insulin resistance, in part due to higher SC fat and lower physical activity, and had higher triglyceride levels and lower HDL and sex hormone binding globulin levels.

Dunaif et al. (1054-P) reported studies of an allelic variation on chromosome 19p closely linked to the insulin receptor gene associated with PCOS. Women with PCOS positive for this allele had increased glucose without compensatory hyperinsulinemia, while brothers of women with PCOS who had the allele had high proinsulin levels, suggesting β-cell dysfunction. Hirschler et al. (1763-P) studied 74 obese Hispanic adolescents with mean age 12 years, 55% with acanthosis nigricans, with the physical finding showing strong correlation with the degree of obesity but not with glucose intolerance or insulin resistance per se. In a small study, Sellers et al. (1765-P) raised important caution about the use of metformin in children with type 2 diabetes. The authors randomized 18 children who had been treated without drugs for at least 3 months and who had HbA_{1c} >7% to either metformin, titrated slowly to a maximum of 2,250 mg daily, or placebo. HbA_{1c} and BMI were the same in both groups at 3, 6, and 12 months; five and four children in the metformin and placebo groups, respectively, required addition of insulin, and four in each group had <50% compliance. Side effects were ob-

served in four of the subjects who received metformin but in none of the subjects in the placebo group.

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AHA Scientific Statement

Obesity, Insulin Resistance, Diabetes, and Cardiovascular Risk in Children

An American Heart Association Scientific Statement From the Atherosclerosis, Hypertension, and Obesity in the Young Committee (Council on Cardiovascular Disease in the Young) and the Diabetes Committee (Council on Nutrition, Physical Activity, and Metabolism)

This statement was reviewed by the American Diabetes Association. The recommendations contained herein are consistent with the American Diabetes Association's Clinical Practice Recommendations.

Julia Steinberger, MD; Stephen R. Daniels, MD, PhD

Atherosclerotic cardiovascular disease is the No. 1 killer in the adult population of Western societies,[1] but the pathological processes and risk factors associated with its development have been shown to begin during childhood.[2] Obesity plays a central role in the insulin resistance syndrome, which includes hyperinsulinemia, hypertension, hyperlipidemia, type 2 diabetes mellitus, and an increased risk of atherosclerotic cardiovascular disease. The incidence of type 2 diabetes reported in children has increased alarmingly.[3,4]

Resistance of the body to the actions of insulin results in increased production of this hormone by the pancreas and ensuing hyperinsulinemia. Obesity beginning in childhood often precedes the hyperinsulinemic state. Other components of the insulin resistance syndrome are also present in children and adolescents.[5,6] An association between obesity and insulin resistance has been reported in the young, as has the link between insulin resistance, hypertension, and abnormal lipid profile. There is an increasing amount of data showing that being overweight during childhood and adolescence is significantly associated with insulin resistance, dyslipidemia, and elevated blood pressure in young adulthood. Weight loss by obese youngsters results in a decrease in insulin concentration and improvement in insulin sensitivity. Moreover, it has been determined that increased left ventricular mass, which is an independent risk factor for cardiovascular disease in adults, is present in childhood. Recent research has found that left ventricular hypertrophy is related to other risk factors, including obesity and insulin resistance in children and adolescents.[7] The specifics of the transition from risk factors in childhood to diabetes and cardiovascular disease are not clear, but compelling evidence points to their association with overt disease in adults. On the basis of current knowledge and extrapolation from studies in adults, it is reasonable to suggest that lifestyle modification and weight control in childhood could reduce the risk of developing the insulin resistance syndrome, type 2 diabetes mellitus, and cardiovascular disease.

Obesity and the Insulin Resistance Syndrome

Obesity increases the risk of cardiovascular disease in adults and has been strongly associated with insulin resistance in normoglycemic persons and in individuals with type 2 diabetes.[8,9]

Data from the Framingham study have established an increased incidence of cardiovascular events with increasing weight in both men and women.[10] Body weight and mortality were directly related in the Harvard Alumni Health Study,[11] and weight gain was a significant risk factor for development of diabetes mellitus in women.[12] The association of obesity with the insulin resistance syndrome and cardiovascular risk is not only related to the degree of obesity but also seems to be critically dependent on body fat distribution. Thus, individuals with greater degrees of central adiposity develop this syndrome more frequently than do those with a peripheral body fat distribution.[13]

Studies in obese adults have shown sustained improvement in cardiovascular risk in association with a 10% to 15% weight loss maintained over time.[14] One other report, however, suggested that a weight loss of 16% resulted in a

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differential risk factor response, including a dramatic reduction in the incidence of type 2 diabetes but not in the 8-year incidence of hypertension.[15]

An association between adiposity and insulin resistance has been reported in adults and children.[16,17] Weight loss is associated with a decrease in insulin concentration and an increase in insulin sensitivity in adults[18] and adolescents.[19] In a study of 122 adolescents, obese individuals were significantly more insulin resistant and had an abnormal lipid profile when compared with lean subjects[5]; in this study, insulin resistance was significantly related to an abnormal lipid profile in heavy children but not in thin children, and insulin resistance varied directly with the degree of adiposity. Obesity and insulin resistance have also been shown to be associated with other risk factors, such as elevated blood pressure. Ethnic and sex differences occur in the insulin resistance syndrome in the United States, with a greater prevalence demonstrated in men and in African Americans.[20]

Hypertension and the Insulin Resistance Syndrome

Essential hypertension is the clinical expression of a disordered interaction between the genetic, physiological, and biochemical systems that under usual conditions maintain cardiovascular homeostasis. The multifactorial nature of essential hypertension has made it difficult to completely isolate the action of any one of these systems from the actions of the others.

The relation between insulin metabolism/resistance and essential hypertension has the potential to provide insight into the mechanisms that operate this complex interaction.[21–25] Insulin increases renal sodium retention[26–29] while increasing free water clearance. Insulin resistance is also associated with increased sympathetic nervous system activity[30] and stimulation of vascular smooth muscle growth.[31] Insulin levels have been found to be significantly higher in adult patients with essential hypertension[32–34] and borderline hypertension[35] than in normotensive control patients. This is true whether insulin is measured in the fasting state[32–34,35] or in response to the oral glucose tolerance test,[32–34] the insulin suppression test, or the euglycemic insulin clamp technique.[33,35] Moreover, these differences have been reported to be independent of age, sex, and ethnic group.[32–35] A confounding factor in the insulin–hypertension link is obesity. In most of the world's populations, blood pressure is directly correlated with body weight. Numerous studies have confirmed the association between weight gain, percent body fat, and insulin resistance.[21,36–39] Other studies, however, have indicated that an interaction exists between insulin and hypertension that is independent of their interaction with obesity.[40] The Coronary Artery Risk Development In young Adults (CARDIA) study of 4576 young adults reported a weight-independent association between fasting insulin concentration and hypertension.[41] Thus, it is clear that several questions about the association between blood pressure and the syndrome of insulin resistance remain unanswered. Although the prevalence of essential hypertension in children is low, the precursors of this disease are present long before clinically accepted levels of hypertension are recognized. Substantial evidence from genetic and epidemiological studies confirms that blood pressure tracks over time and that the roots of essential hypertension extend into the first and second decades of life.[42,43]

There is a strong genetic influence on blood pressure that in some can be identified early in childhood[44] and that is intensified in the presence of other risk factors.[45] Several studies have addressed the association between insulin and blood pressure in children and adolescents. Interactions similar to those identified in adults also may be found at a young age. The Bogalusa Heart Study has shown a positive correlation between blood pressure and fasting insulin, even after adjustment for body mass index, as early as 5 years of age.[46] Insulin resistance has been found in young black men (early twenties) with only borderline hypertension, independent of body mass index.[35] Several mechanisms through which blood pressure may be linked with insulin resistance have been proposed. In adolescents, the resistance to insulin has been associated with chronic sodium retention[47] and sodium sensitivity,[48] and this is reversible with weight loss and exercise.[18] Moreover, obese, insulin-resistant adolescents have increased forearm vascular resistance that is reversible with weight loss.[49] Of particular interest, normotensive adolescent offspring (mean age of 13 years) of hypertensive parents were found to have significantly higher serum insulin levels after an overnight fast and an intravenous glucose load, which suggests that insulin resistance predates an increase in blood pressure in subjects with a genetic predisposition to hypertension.[50] Because multiple mechanisms contribute to the development of hypertension, it is difficult to isolate the contribution of obesity and/or hyperinsulinemia.

Lipid Abnormalities and the Insulin Resistance Syndrome

Insulin resistance has been hypothesized to play a major role in dyslipidemia in individuals with normal glucose tolerance, as well as in those with impaired glucose tolerance and type 2 diabetes.[51,52] Lipid abnormalities have also been reported in obese adults, who have elevated triglycerides and LDL cholesterol and low levels of HDL cholesterol.[53,54] Similar lipid profiles have been reported in obese and nonobese adults with type 2 diabetes, in obese normoglycemic adults, and in nonobese adults with impaired glucose tolerance.[55–57] The association between obesity and dyslipidemia observed in adults also has been documented also in children and adolescents. In the Lipid Research Clinics Population Studies Data Book, obese adolescents had an abnormal "atherogenic" lipid profile consisting of elevated LDL cholesterol and triglycerides and low HDL cholesterol. In more recent studies in children, insulin resistance was also implicated in the association between obesity and dyslipidemia. In a study of insulin resistance and lipids that compared 82 normoglycemic, obese adolescents with 40 lean adolescents, abnormalities consistent with an atherogenic lipid profile were present in the obese subjects. The dyslipidemia correlated with the degree of insulin resistance in the obese children, and it was shown that the degree of insulin resistance explained a significant portion of the variance in the levels of triglycerides, LDL cholesterol, and HDL cholesterol.[5] Investigators from the Bogalusa Heart Study reported that overweight schoolchildren, in comparison with their lean counterparts,

were 2.4 to 7.1 times more likely to have elevated total cholesterol, LDL cholesterol, and triglycerides, and 12.6 times more likely to have hyperinsulinemia.[58]

Several mechanisms whereby insulin resistance could cause an alteration in lipid metabolism have been described. Hyperinsulinemia is known to enhance hepatic very-low-density lipoprotein synthesis and thus may directly contribute to the increased plasma triglyceride and LDL cholesterol levels.[59] Resistance to the action of insulin on lipoprotein lipase in peripheral tissues may also contribute to elevated triglyceride and LDL cholesterol levels.[60,61] It has been suggested that insulin resistance may be responsible for the reduced levels of HDL cholesterol observed in type 2 diabetes patients and that despite enhanced HDL cholesterol synthesis, the plasma HDL cholesterol concentration was significantly reduced in patients with type 2 diabetes versus control subjects; this decrease in plasma HDL cholesterol was accounted for entirely by an increase in the rate of apolipoprotein A1/HDL cholesterol degradation, which exceeded the enhanced rate of its synthesis.[62]

Other intrinsic metabolic factors, such as apolipoproteins, lipoprotein A, and homocysteine, are known to influence the development of cardiovascular disease; their potential relationship to the insulin resistance syndrome remains to be clarified.

Assessment

Our understanding of the insulin resistance syndrome in children is evolving, and there is no general agreement about the overall assessment and treatment of this syndrome. Although the end points for cardiovascular risk are not seen in childhood, the components of the insulin resistance syndrome (obesity, hypertension, dyslipidemia, and hyperinsulinemia) track from childhood into adulthood, which supports the conclusion that the precursors of cardiovascular disease are present early in life.[63,64] Because insulin resistance often is associated with type 2 diabetes, the first step in assessment is to identify children who would benefit from intervention. Testing has been recommended for children at significant risk for the presence or development of type 2 diabetes.[65] These are children who in general: (1) are overweight; (2) have a family history of type 2 diabetes; (3) have a predisposition based on race/ethnicity (American Indian, African American, Hispanic, Asian/Pacific Islander); and (4) have signs of insulin resistance or conditions associated with insulin resistance (eg, acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome). The diagnosis of diabetes can be made by using either the fasting plasma glucose or the 2-hour value on an oral glucose tolerance test. The fasting glucose determination is preferred. At this time, sufficient data are not available to support the use of the $HbA1_c$ in the diagnosis of diabetes. It is important to remember that even in the face of a normal fasting glucose level, the child may have diabetes or remain at risk for developing type 2 diabetes.

Children who do not have elevated blood glucose concentrations may exhibit other features of the insulin resistance syndrome, such as obesity, hypertension, and high cholesterol, and they remain at risk for cardiovascular disease and diabetes. Body size measurements (expressed by body mass index, waist circumference [a measure of central adiposity], or other methods) and determination of blood pressure and cholesterol should become part of the evaluation of any child with the risk profile described above. Insulin resistance is measured by an accurate but rather complicated method: the euglycemic insulin clamp. This technique involves the continuous intravenous administration of insulin and glucose over 3 hours and the calculation of insulin sensitivity (the inverse of insulin resistance) by measuring the amount of glucose required to maintain normal glucose levels (euglycemia).[66] The euglycemic clamp currently is used for research purposes only. Although less accurate than the euglycemic clamp method, assessment of hyperinsulinemia from fasting plasma insulin levels and estimation of insulin resistance from indices based on fasting glucose and insulin levels have been proposed as reasonable alternative methods for evaluating insulin resistance.

Type 2 Diabetes Mellitus in Children and Adolescents

Type 2 diabetes mellitus has long been considered a disease of adults, in whom it is the most prevalent form of diabetes (≈90%) and is associated with increased risk of cardiovascular disease morbidity and mortality.[67] During the past 10 years, however, an increasing frequency in the occurrence of type 2 diabetes mellitus has been reported in adolescents.[3] There are now reports in the literature of type 2 diabetes in Native American, Hispanic, African-American, South Asian, and white youth.[4] This increase in frequency of type 2 diabetes seems to parallel the increase in prevalence and severity of obesity in children and adolescents.[68]

Type 2 diabetes is often asymptomatic in its early stages. This makes the diagnosis difficult without an awareness of the subtle characteristics that should prompt further work-up. Some patients are diagnosed with the typical symptoms of polyuria and polydipsia, and some develop ketoacidosis.[69] Others are asymptomatic or may have nonspecific findings, such as vaginal moniliasis.[3] Some patients are identified when glycosuria is found on routine testing for sports, school, or employment examinations.[4] Obesity, acanthosis nigricans, and a positive family history of diabetes are common in adolescents with type 2 diabetes. At diagnosis, the fasting C peptide and insulin concentrations are often elevated, and antibodies to pancreatic islet cells are generally absent.[70] Glycosylated hemoglobin concentrations may be elevated but variable according to how early in the course of the disease the diagnosis is made.[71,72] Children with type 2 diabetes are usually diagnosed after age 10 years. This may be in part due to the physiological insulin resistance seen with the hypersomatotropic state of puberty, which may contribute to the exacerbation of the disease. Adolescents with type 2 diabetes mellitus are almost always obese. The mean body mass index in clinical series has ranged from 26 to 38 kg/m^2.[4] Patients with type 2 diabetes often have other risk factors for cardiovascular disease. The prevalence of elevated blood pressure has ranged from 17% to 32%. The prevalence of hypertriglyceridemia has ranged from 4% to 32%.[4] In one study, 6% had a clinical diagnosis of sleep apnea.[3]

Because type 2 diabetes is a relatively recent problem in adolescents, few data on long-term follow-up exist. One study of Pima Indians monitored 36 individuals for a mean of 10 years until they reached a median age of 26 years. In this cohort, at baseline (age 5 to 19 years), 85% were obese, 14% had hypertension, 30% had total cholesterol >200 mg/dL, and 55% had triglyceride concentrations >200 mg/dL. Fifty-eight percent of the patients had microalbuminuria and 16% a urinary albumin/creatinine ratio >300 mg/g, which indicated that the renal effects of diabetes were already present at diagnosis. After 10 years of follow-up, the number of patients with increased urinary albumin excretion was significantly increased, as was the magnitude of albuminuria.[73] Thus, these patients have a constellation of risk factors that place them at increased risk of cardiovascular disease at an early age.

The pathophysiology of the development of type 2 diabetes mellitus is complex and multifactorial. It is believed that obesity leads to insulin resistance and increased circulating insulin concentrations over time. It seems that at some point a loss of control of blood glucose begins to emerge, resulting in dietary glucose intolerance. This ultimately results in type 2 diabetes. It is known that obese individuals may develop different degrees of insulin resistance, and not all individuals develop glucose intolerance. The factors that make some individuals more likely to progress to type 2 diabetes mellitus are not well understood at the present time. A strong family predisposition is known to exist; therefore, parental history is important in risk assessment. In the future, genetic markers may help identify those offspring of diabetic parents who are greatest risk of developing diabetes.

The treatment of type 2 diabetes mellitus in adolescents is similar to the treatment in adults. Because obesity is the major underlying factor, patients are counseled on an improved, calorie-restricted diet and increased physical activity to achieve better energy balance and weight loss. It is not currently known what level of weight loss is necessary for adolescents to achieve improved glucose handling. In adults, it seems that a 10% to 15% weight loss has substantial benefit. Patients may also be treated with oral agents. Future studies may answer questions about the safety and efficacy of oral agents in children in general, and specifically about the safety and efficacy of medications that increase insulin sensitivity, such as glitazones. Some adolescents with type 2 diabetes mellitus may require administration of insulin to achieve control of their diabetes.

Type 2 diabetes mellitus seems to be emerging as a major public health problem for adolescents. The early onset of type 2 diabetes suggests that these patients will be at risk for the development of cardiovascular disease at a young age. If the secular trend seen with increasing prevalence and severity of obesity in childhood and adolescence continues, it is likely that the problem of type 2 diabetes also will increase in the pediatric age group.[74]

Significance

In the face of the major impact that adult cardiovascular disease has in the westernized societies, it seems crucial to examine further the relationships among cardiovascular risk factors at the childhood–adolescence–adulthood transition, ie, the putative earliest point in the development of cardiovascular risk. This may result in important information on the etiologic relations between early indicators of the insulin resistance syndrome, type 2 diabetes, and establishment of risk in young adulthood.

As more research evidence is accumulated, it is also important to deal with the problems of insulin resistance and type 2 diabetes in children and adolescents from a clinical standpoint. The first approach should focus on prevention of obesity in childhood. More attention should be paid to increasing physical activity and decreasing calorie consumption in this age group. Once obesity is established in a child or adolescent, vigorous clinical efforts should be directed at treating it. At present, this involves therapy directed at behavior change, but in the future it may include pharmacological and surgical approaches in the appropriate patients. Clinicians should watch vigilantly for the subtle signs that indicate the development of insulin resistance, glucose intolerance, and type 2 diabetes. Early recognition of these problems can lead to better treatment. On the basis of current knowledge, it seems that better control of blood glucose is likely to lead to improved long-term microvascular and macrovascular outcomes. Thus, the best approach to prevention of future cardiovascular disease in these young patients is early recognition and aggressive therapy. Without this, it is likely that this patient population is destined to develop cardiovascular complications and require substantial resources for future management.

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KEY WORDS: AHA Scientific Statements ■ pediatrics ■ cardiovascular diseases ■ obesity ■ diabetes mellitus

Impaired Microvascular Function in Obesity

Implications for Obesity-Associated Microangiopathy, Hypertension, and Insulin Resistance

Renate T. de Jongh, MD; Erik H. Serné, MD, PhD; Richard G. IJzerman, MD; Greetje de Vries; Coen D.A. Stehouwer, MD, PhD

Background—Obesity is associated with an increased risk of developing microangiopathy, hypertension, and insulin resistance. We hypothesized that obesity is a primary cause of microvascular dysfunction, which may contribute to the development of these obesity-related disorders.

Methods and Results—We examined microvascular function in 16 lean (body mass index <24 kg/m^2) and 12 obese (body mass index >30 kg/m^2) healthy women (mean age, 38.9±6.7 years) in the basal state and during physiological systemic hyperinsulinemia. We determined skin capillary recruitment after arterial occlusion with capillaroscopy and skin endothelium–(in)dependent vasodilation by iontophoresis of acetylcholine and sodium nitroprusside. Obese women, compared with lean women, had higher systolic blood pressure ($P<0.05$), impaired insulin sensitivity ($P<0.01$), impaired capillary recruitment in the basal state ($P<0.05$) and during hyperinsulinemia ($P<0.05$), and impaired acetylcholine-mediated vasodilation in the basal state ($P<0.05$) and during hyperinsulinemia ($P<0.01$). Sodium nitroprusside–mediated vasodilation was similar in lean and obese women. Capillary recruitment and acetylcholine-mediated vasodilation were positively correlated with insulin sensitivity ($r=0.58$, $P<0.01$ and $r=0.55$, $P<0.01$, respectively) and negatively with blood pressure ($r=-0.64$, $P<0.001$ and $r=-0.42$, $P<0.05$, respectively) in both lean and obese women.

Conclusions—Obesity is characterized by impaired microvascular function in the basal state and during hyperinsulinemia and, in both lean and obese women, microvascular dysfunction is associated with increased blood pressure and decreased insulin sensitivity. These findings are consistent with a contribution of impaired microvascular function to the development of obesity-related microangiopathy, hypertension, and insulin resistance. (***Circulation.*** **2004;109:2529-2535.)**

Key Words: microcirculation ■ obesity ■ insulin

The current obesity epidemic implies that obesity is becoming an increasingly important risk factor for cardiovascular disease.[1,2] This is the case not only for large-artery disease, such as myocardial infarction and stroke,[1,3] but also for disease entities that are caused wholly or in part by microangiopathy, notably retinopathy, nephropathy, and heart failure.[4–7]

How obesity causes large-artery disease and microangiopathy is poorly understood. In part, these may be the consequences of obesity-associated hypertension, insulin resistance, and dyslipidemia, but these risk factors cannot entirely explain the association of obesity with large-artery disease and microangiopathy.[5,6]

We hypothesized that obesity may be a primary cause of microvascular dysfunction and that this has several pathophysiological consequences. First, it may constitute a pathway through which obesity increases blood pressure and decreases insulin sensitivity. In addition, it may directly contribute to obesity-associated microangiopathy. Indeed, there is some evidence that measures of obesity in healthy individuals are associated with impaired microvascular function.[8] In addition, microvascular dysfunction has been shown to increase peripheral vascular resistance and antedate the development of hypertension, indicating a role for microvascular dysfunction in the development of hypertension.[9–11] Finally, microvascular dysfunction in the basal state and during hyperinsulinemia has been proposed to partially explain defects in the ability of insulin to increase glucose uptake in insulin-resistant states such as hypertension and obesity,[12,13] because impaired recruitment of nutritive capillaries in muscle during physiological hyperinsulinemia may impair glucose delivery and uptake.[14]

In view of these considerations, we hypothesized that obesity is characterized by impaired microvascular function in the basal state and during physiological hyperinsulinemia and that such impairments may contribute to the development of obesity-associated microangiopathy, hypertension, and

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From the Department of Medicine (R.T.J., E.H.S., R.G.I.J., G.V., C.D.A.S.), VU University Medical Center, Amsterdam, Netherlands, and Institute for Cardiovascular Research, Vrije Universiteit (R.T.J., E.H.S., R.G.I.J., C.D.A.S.), Amsterdam, Netherlands.

Correspondence to Prof Dr Coen D.A. Stehouwer, Department of Internal Medicine, University Hospital Maastricht, PO Box 5800, 6202 AZ Maastricht, The Netherlands.

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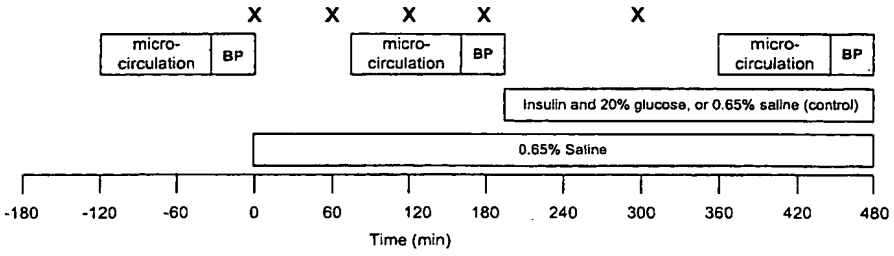

Figure 1. Design of study. Microcirculation indicates microvascular measurements; BP, blood pressure measurements; X, blood sample. For comparison between lean and obese women, insulin and FFA concentrations are mean of 6 measurements at t=0, 60, 120, and 180 minutes on insulin study day and t=0 and 180 minutes on saline study day. Glucose concentrations are mean of 4 measurements at t=0 and 180 minutes on both study days. For analyses within both study days, insulin and glucose concentrations are mean of concentrations at t=0 and 180 minutes. Insulin concentrations during clamps are measured at t=300 minutes.

insulin resistance. To investigate this, we examined microvascular function in the basal state and during physiological hyperinsulinemia in lean and obese women.

Methods

Subjects

We included 16 lean (body mass index <24 kg/m^2) and 12 obese (body mass index >30 kg/m^2) women. Volunteers were recruited through advertisements in newspapers. Participants were healthy as judged by medical history, nondiabetic,[15] normotensive (<140/90 mm Hg) as determined by triplicate office blood pressure measurement, nonsmokers, and they did not use any medication except oral contraceptives. All participants gave informed consent for participation in the study. The study was undertaken with approval of the local ethics committee and performed in accordance with the Declaration of Helsinki.

Study Design

All individuals underwent the study protocol as shown in Figure 1. All measurements were conducted in a fasting state on an outpatient basis in a quiet, temperature-controlled room (23.4±0.5°C) and after 30 minutes of acclimatization. The 0.65% saline infusion served as a control for a study of the effects of a lipid infusion on microvascular function; these results are not reported in the present article.

Hyperinsulinemic, Euglycemic Clamp

Insulin sensitivity was determined with the hyperinsulinemic, euglycemic clamp method as described previously,[16] with an insulin infusion rate of 40 mU · m^{-2} · min^{-1}. The M-value is defined as the glucose infusion rate during the second hour of the clamp expressed per kilogram of body weight. The M/I value is the M-value expressed per unit of plasma insulin concentration. A time- and volume-control study was performed in an identical manner at a later date.

Skin Microvascular Measurements

Nailfold capillary studies were performed as described previously.[8,13,17] Briefly, nailfold capillaries in finger skin were recorded before and after 4 minutes of arterial occlusion with a digital cuff. This procedure was performed twice, and the mean of both measurements was used for analyses. We estimated baseline capillary density by counting the number of continuously erythrocyte-perfused capillaries during a 15-second period. Other capillaries can be seen to be intermittently perfused, and these may represent an important functional reserve. We used postocclusive reactive hyperemia to estimate this functional reserve. Postocclusive capillary recruitment was calculated by dividing the increase in density by the baseline density. The day-to-day coefficient of variation of postocclusive capillary recruitment was 15.9±8.0%, as determined in 10 individuals on 2 separate days.

Microvascular endothelium–(in)dependent vasodilation was evaluated with laser Doppler flowmetry together with iontophoresis of acetylcholine (ACh) and sodium nitroprusside (SNP) as described previously.[8,13,17] The day-to-day coefficient of variation was 12.2±9.7% for ACh-mediated vasodilation and 16.4±8.1% for SNP-mediated vasodilation, as determined in 10 individuals on 2 separate days. To exclude possible nonspecific microvascular reactivity, we studied the effects of hyperinsulinemia on vehicle responses of ACh (mannitol 3%) and SNP (water for injection).

Blood Pressure

Ambulatory 24-hour blood pressure monitoring (Spacelabs 90207) was performed as described previously.[8,13] One of the obese women did not complete the measurement because of intolerance to the continuous presence of the cuff around the arm. During study days, blood pressure measurements were determined as depicted in Figure 1 (Colin Press-Mate BP-8800). The average of 3 measurements during each period was used for further analyses.

Statistical Analyses

Data are expressed as mean±SD or median (interquartile range) as appropriate. To examine differences in microvascular function between lean and obese women, we used the mean of 2 microvascular measurements, ie, the first 2 measurements on the insulin study day (Figure 1). (The use of the mean of the first 2 microvascular measurements on the saline study day gave similar results.) For analysis of associations, we used the mean of 4 microvascular measurements, ie, the first 2 measurements on both the insulin and saline study days (Figure 1).

The distribution of variables was tested for normality. A nonpaired Student's *t* test was used to compare lean with obese women and a paired Student's *t* test to compare insulin with saline infusion. The Wilcoxon signed-rank test for 2 related samples was used to examine insulin-mediated effects on vehicle responses. Multiple regression analysis was used to investigate confounding by systolic blood pressure, blood lipid concentrations, oral contraceptive use, or menstrual phases and to study associations with adjustment for age. Interaction analysis was performed to study whether associations were different between lean and obese women. A 2-tailed probability value of $P<0.05$ was considered significant.

Results

Characteristics of Lean and Obese Women

Obese women had lower HDL cholesterol and higher triglyceride, free fatty acid, insulin, and glucose concentrations and were more insulin resistant than lean women (Table 1). Although all individuals were normotensive, systolic blood pressure was higher in obese women.

Metabolic and Hemodynamic Variables Before and During Insulin and Saline Infusion in Lean and Obese Women

Compared with saline infusion, blood glucose concentrations increased during insulin infusion in lean women, because glucose concentrations were clamped at 5 mmol/L (0.6±0.6 versus −0.1±0.9 mmol/L, $P<0.05$) (Table 2).

TABLE 1. Characteristics of Both Study Groups

	Lean Women (n=16)	Obese Women (n=12)
Age, y	39.0±6.7	38.8±7.0
Weight, kg	61.1±8.3	111.2±19.6†
BMI, kg/m^2	21.3±1.9	38.5±6.6†
WHR	0.78±0.06	0.92±0.07†
Serum cholesterol, mmol/L	5.1±0.5	5.1±0.8
Serum LDL cholesterol, mmol/L	2.8±0.4	2.9±0.7
Serum HDL cholesterol, mmol/L	2.0±0.6	1.5±0.3*
Serum triglycerides, mmol/L	0.8±0.3	1.4±0.8†
Plasma FFAs, μmol/L	0.44±0.08	0.65±0.12†
Plasma insulin, pmol/L	30±8	82±30†
Blood glucose, mmol/L	4.3±0.4	4.8±0.4†
M/I value (mg · kg^{-1} · min^{-1} · pmol · L^{-1})×100	2.1±1.0	0.5±0.3†
24-Hour systolic blood pressure, mm Hg	115±8	123±7*
24-Hour diastolic blood pressure, mm Hg	72±7	70±6
24-Hour heart rate, bpm	79±11	82±8

BMI indicates body mass index; WHR, waist-to-hip ratio; M/I value, glucose infusion rate during the second hour of the hyperinsulinemic clamp expressed per kilogram body weight and per unit of plasma insulin concentration.
*$P<0.05$, †$P<0.01$.

Microvascular Function Is Impaired in Obese Compared With Lean Women

There were no differences in baseline perfused capillary density between lean and obese women (Table 3). Postocclusive capillary recruitment was diminished in obese women ($P<0.05$) (Table 3; Figure 2). Iontophoresis of ACh induced a lower relative increase in perfusion in obese than in lean women ($P<0.05$). SNP-mediated vasodilation was not different between the 2 groups ($P=0.7$).

Compared with lean women, obese women had dyslipidemia and increased systolic blood pressure (Table 1). Multiple regression analysis demonstrated that adjustment for free fatty acids (FFAs) did not materially affect the association of obesity with either impaired capillary recruitment (β, −16.2 versus −16.3 percentage points) or ACh-mediated vasodilation (β, −147.2 versus −144.6 percentage points). Adjustment for HDL cholesterol or triglyceride concentrations also gave similar results (data not shown). Adjustment for systolic blood pressure did not change the association between obesity and impaired capillary recruitment (β, −16.8 versus −16.3 percentage points) but reduced the association between obesity and impaired ACh-mediated vasodilation by 38% (β, −89.4 versus −144.6 percentage points). The associations did not change materially if the use of oral contraceptives or phase of the menstrual cycle (follicular or luteal) was added to the model (data not shown).

Microvascular Function Is Associated With Blood Pressure and Insulin Sensitivity in Lean and Obese Women

Figure 3 shows that decreased capillary recruitment and ACh-mediated vasodilation were associated with both increased 24-hour systolic blood pressure and decreased insulin sensitivity in lean and obese women. Interaction analysis indicated that these associations were not significantly influenced by the presence of obesity (data not shown). The use of the M value instead of the M/I value did not lead to different conclusions (data not shown).

Insulin-Induced Changes in Microvascular Function Are Impaired in Obese Compared With Lean Women

Compared with saline infusion, insulin infusion did not change baseline perfused capillary density but increased postocclusive capillary recruitment in lean (15.4±13.4 versus −0.4±8.7 percentage points, $P<0.001$) and obese women (17.4±12.2 versus 2.3±6.1 percentage points, $P<0.01$) (Table 3; Figure 2). Although these insulin-induced increases in postocclusive capillary recruitment were not significantly

TABLE 2. Metabolic and Hemodynamic Variables Before and During Infusions of Insulin and Saline

	Insulin		Saline	
	Before Infusion	During Infusion	Before Infusion	During Infusion
Lean women				
Blood glucose, mmol/L	4.2±0.4	4.9±0.4†‡	4.3±0.3	4.2±0.5
Plasma insulin, pmol/L	25±10	378±102†§	24±8	19±8†
Systolic blood pressure, mm Hg	118±14	117±12	119±9	120±15
Diastolic blood pressure, mm Hg	65±9	63±7	64±9	67±9
Heart rate, bpm	67±11	68±21	66±12	70±14†
Obese women				
Blood glucose, mmol/L	4.7±0.6	5.0±0.2	4.8±0.5	4.7±0.6
Plasma insulin, pmol/L	79±30	483±187†§	84±31	63±28†
Systolic blood pressure, mm Hg	128±8	135±8*‖	130±10	135±11†
Diastolic blood pressure, mm Hg	70±9	74±9‖	70±7	75±6†
Heart rate, bpm	70±6	80±6†	72±6	76±6†

* $P<0.05$, †$P<0.01$ during vs before infusion; ‡$P=0.05$, §$P<0.01$ change during insulin vs saline infusion; ‖$P<0.05$ change in obese vs lean women.

TABLE 3. Microvascular Measurements Before and During Infusions of Insulin and Saline

	Insulin		Saline	
	Before Infusion	During Infusion	Before Infusion	During Infusion
Lean women				
Capillary density				
Baseline density, n/mm²	38.2±5.0	38.2±6.7	37.1±5.3	35.9±5.9
Peak density, n/mm²	58.3±0.7.7	63.8±9.6§‖	57.4±8.3	55.9±8.9
Percentage increase, %	56.2±19.3	72.4±25.1§‖	57.8±19.3	57.4±15.7
ACh-mediated vasodilation				
Baseline skin perfusion, PU	24.7±5.6	25.6±10.0	28.0±6.1	31.4±10.5
Plateau, PU	154.2±48.9	199.3±88.3	161.9±59.2	171.4±82.3
Percentage increase, %	537±133	685±199§‖	489±180	434±157
SNP-mediated vasodilation				
Baseline skin perfusion, PU	30.4±8.9	31.9±16.4	31.7±10.3	32.3±14.8
Plateau, PU	160.9±48.9	160.1±60.3	136.2±63.2	171.4±82.8
Percentage increase, %	476±186	450±220	371±224	368±248
Obese women				
Capillary density				
Baseline density, n/mm²	38.6±5.7	37.4±5.2	37.7±3.7	37.3±3.9
Peak density, n/mm²	52.5±7.7	56.6±5.0*	54.0±4.6	54.3±4.1
Percentage increase, %	37.4±9.3*	54.8±15.4*§‖	44.7±14.8	47.0±12.6
ACh-mediated vasodilation				
Baseline skin perfusion, PU	25.6±8.5	26.3±12.4	26.0±9.0	24.8±7.0
Plateau, PU	106.4±40.9*	99.5±44.0†	116.7±44.7	116.0±57.1
Percentage increase, %	345±159*	302±157†	383±265	360±261
SNP-mediated vasodilation				
Baseline skin perfusion, PU	26.8±9.4	25.7±8.1	23.7±9.5	28.6±11.8
Plateau, PU	132.1±57.3	99.0±32.5	114.8±43.8	147.9±81.4
Percentage increase, %	471±301	411±183	451±348	423±221

PU indicates arbitrary perfusion units.

*$P<0.05$, †$P<0.01$ obese vs lean women; ‡$P<0.05$, §$P<0.01$ during vs before infusion; ‖$P<0.01$, change during insulin vs saline infusion.

different ($P=0.8$), postocclusive capillary recruitment during insulin infusion was lower in obese than lean women (54.8±15.4 versus 72.4±25.1%, $P<0.05$).

Compared with saline infusion, insulin infusion did not influence baseline skin perfusion. Insulin infusion augmented ACh-mediated vasodilation in lean (162±116 versus −55±154 percentage points, $P<0.01$) but not in obese women (−43±212 versus −23±207 percentage points, $P=1.0$). The change in obese women was different from that in lean women ($P<0.01$). Insulin or saline infusion did not affect SNP-mediated vasodilation in either lean or obese women. Insulin infusion did not affect the responses to ACh vehicle (median [interquartile range] before versus during insulin infusion, 67% [25%–174%] versus 95% [34%–163%], $P=0.8$; tested in 3 obese and 11 lean women) or SNP vehicle (40% [−16% to 139%] versus 67% [16%–171%], $P=1.0$; tested in 6 obese and 10 lean women).

Similar results were obtained if absolute increases in capillary density and perfusion during iontophoresis of ACh, SNP, and vehicles of both substances were used instead of relative increases (data not shown).

Skin temperature and insulin-mediated changes in skin temperature during microvascular measurements did not differ between lean and obese women (data not shown).

Discussion

The central new finding of this study is that obese, compared with lean, women are characterized by impaired skin microvascular function in the basal state and during physiological hyperinsulinemia. Specifically, we show that in obese women, postocclusive capillary recruitment and microvascular endothelium–dependent vasodilation are decreased; that the insulin-induced increase of microvascular endothelium–dependent vasodilation is abolished; and that, although the insulin-induced increase in postocclusive capillary recruitment is preserved, net postocclusive capillary recruitment during hyperinsulinemia is impaired. In addition, we found that impaired microvascular function is associated with decreased insulin sensitivity and increased blood pressure in both lean and obese women. These findings are consistent with a role for microvascular dysfunction in the development of obesity-related microangiopathy, hypertension, and insulin resistance.

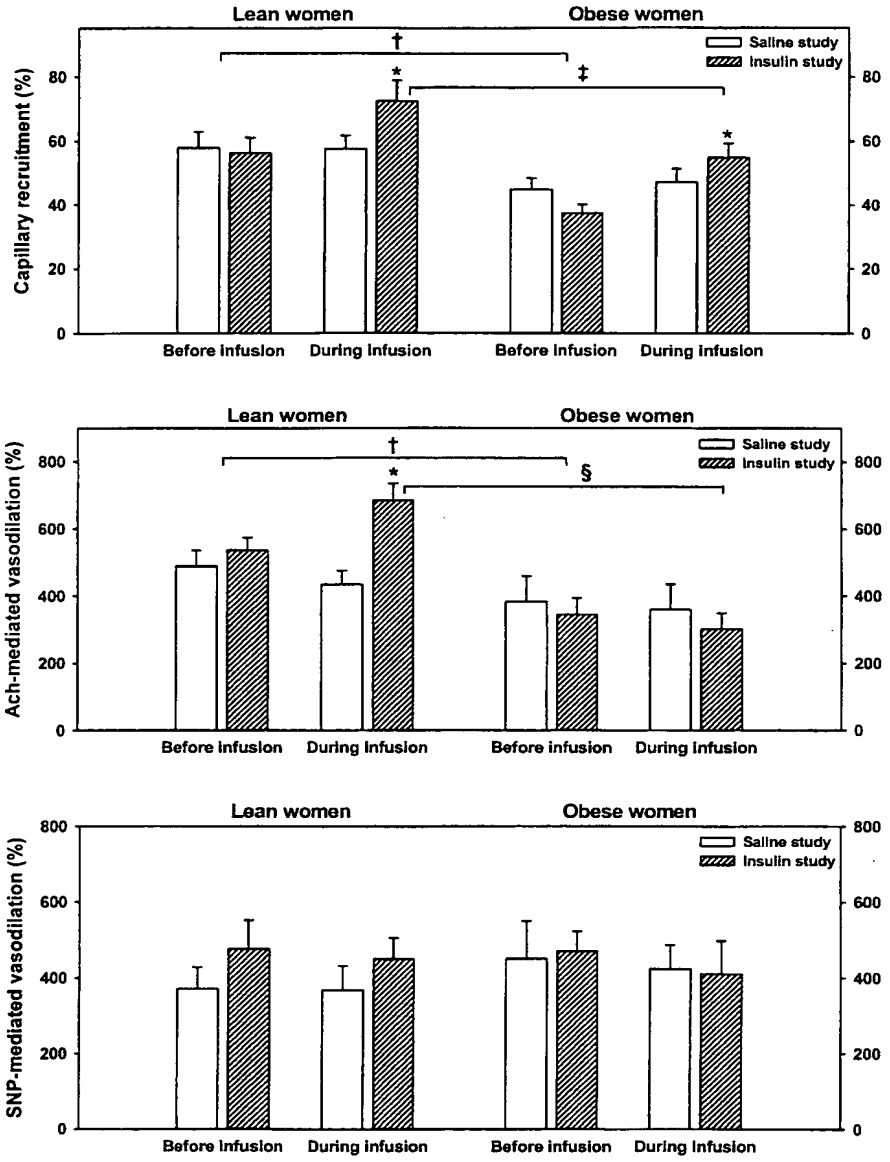

Figure 2. Microvascular measurements before start of infusions and after 2-hour infusions of insulin or saline. *$P<0.05$ during vs before insulin infusion, †$P<0.05$ before infusion in lean vs obese women, ‡$P<0.05$ during infusion in lean vs obese women, §$P<0.01$ insulin-induced change in lean vs obese women.

Our finding of an inverse relationship between microvascular function and blood pressure in both obese and lean women is consistent with a role for microvascular dysfunction in the development of hypertension in obesity and extends previous findings in patients with borderline hypertension,[11] in normotensive and hypertensive lean individuals,[8,13] and in individuals with a familial predisposition to hypertension.[10] Our study was cross-sectional, and we therefore cannot exclude the possibility that microvascular dysfunction was the result of small increases in blood pressure. However, the fact that differences in blood pressure could explain at most a small part of the differences in microvascular function between lean and obese women strongly suggests that presence of obesity is a more important predictor of microvascular dysfunction than blood pressure per se.

We are the first to demonstrate that obesity is associated with microvascular dysfunction both in the basal state and during hyperinsulinemia and that this microvascular dysfunction is related to insulin resistance. These results are consistent with but do not prove a causal link between microvascular dysfunction and impairment of insulin-mediated glucose uptake. Our findings are in agreement with previous studies in resistance vessels.[18,19] However, these studies measured changes in total limb blood flow, whereas recent studies in rats and humans have demonstrated the importance of the microvascular distribution pattern rather than total blood flow.[14] According to this concept,[14] insulin redirects blood flow from nonnutritive vessels to nutritive capillary beds, thereby increasing access of glucose and insulin to muscle cells, independently of changes in total blood flow. Indeed, in rat muscle, infusion of Intralipid or tumor necrosis factor-α (TNF-α) impairs both insulin-induced capillary recruitment and glucose uptake.[20,21] In addition, obese Zucker rats are characterized by both impaired insulin-induced glucose uptake and impaired capillary perfusion in the basal state

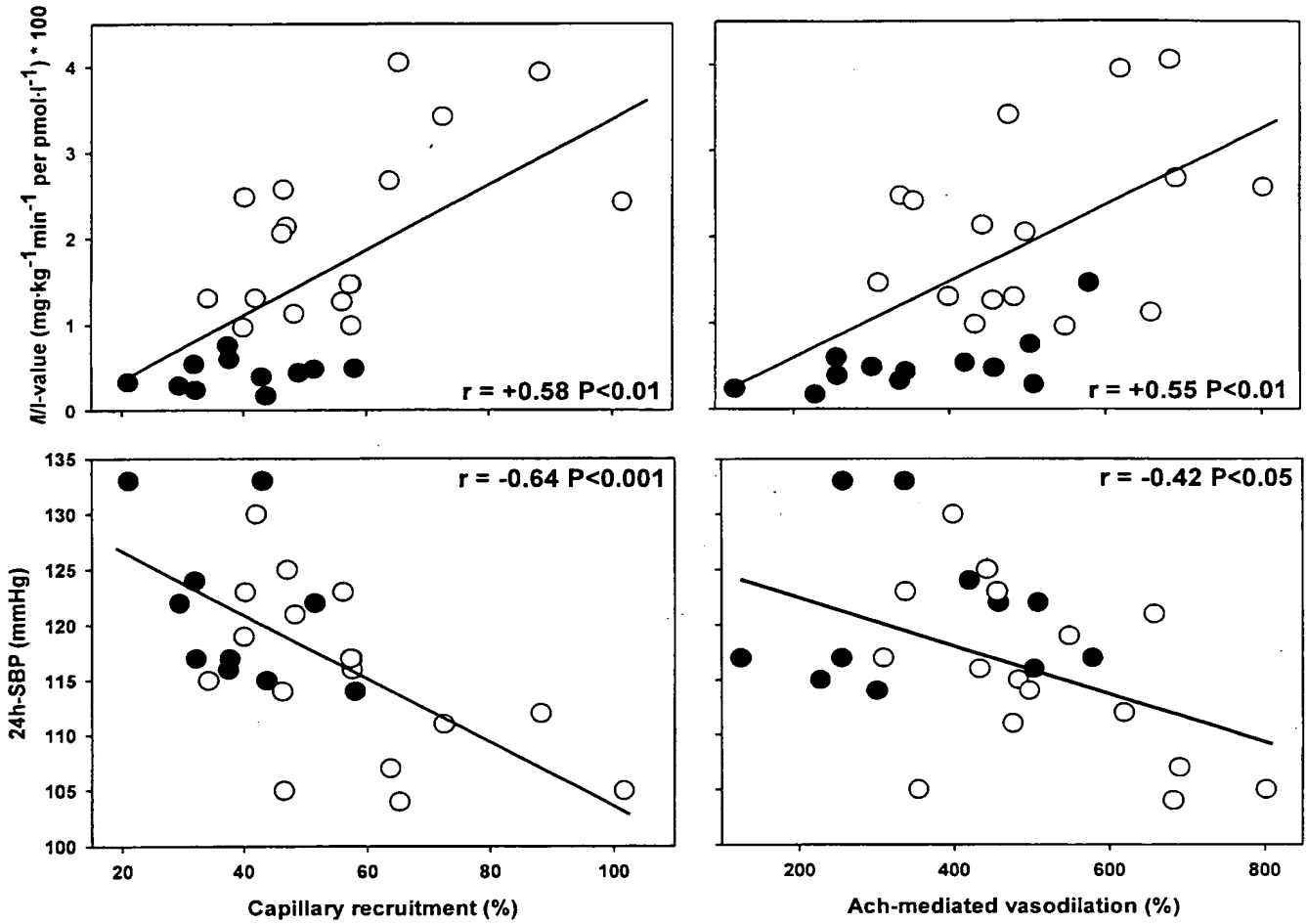

Figure 3. Correlations between capillary recruitment, ACh-mediated vasodilation, 24-hour systolic blood pressure, and insulin sensitivity in lean (open circles) and obese (closed circles) women. Correlation coefficients are adjusted for age.

and during hyperinsulinemia.[12] We now show that this concomitant impairment in insulin sensitivity and microvascular function in the basal state and during hyperinsulinemia is also present in obese women. We also show that microvascular dysfunction in the basal state was significantly associated with reduced insulin-induced glucose uptake in lean and obese women. The latter finding extends previous observations in normotensive and hypertensive individuals.[8,13] Taken together, these data are consistent with a role for microvascular dysfunction in the development of insulin resistance in obesity.

In obese women, the insulin-induced increase of microvascular endothelium-dependent vasodilation was abolished, but the insulin-induced increase in postocclusive capillary recruitment was preserved (Figure 2). The explanation for this discrepancy is not entirely clear. The stimulus used in postocclusive capillary recruitment (ie, increased flow) differs from that used in microvascular endothelium–dependent vasodilation (ie, ACh), and insulin-induced changes in the responses to these stimuli may be differentially sensitive to obesity. In addition, capillary perfusion is thought to be regulated not only by precapillary arteriolar tone and arteriolar vasomotion[14] but also by the characteristics of the capillary network itself.[22]

The pathophysiological mechanism behind the relationship between obesity and microvascular dysfunction is probably multifactorial. Adipose tissue secretes substances, such as FFAs, TNF-α, and adiponectin, that can influence microvascular function. An increase in FFAs impairs vascular function in resistance vessels in humans[23,24] and in microvasculature in rats.[21] Fasting FFA levels were not associated with microvascular function in the present study, but this does not exclude a role for FFA dynamics in modulating microvascular function. In addition, in rats, acute TNF-α elevation impairs insulin-induced capillary recruitment and glucose uptake,[20] and in humans, it concomitantly impairs insulin-induced endothelium-dependent vasodilation in resistance vessels and glucose uptake.[25] Adiponectin levels are reduced in obesity,[26] and adiponectin has a vasoprotective effect, as demonstrated by associations between hypoadiponectinemia and impaired endothelial function in resistance vessels.[27,28] At this point, it should be emphasized that the cross-sectional design of our study does not exclude the possibility that there are as yet unmeasured variables that (in part) explain the association between obesity and microvascular dysfunction, such as physical fitness or diet. These possibilities require further studies.

Although muscle is the main peripheral site of insulin-mediated glucose uptake and vascular resistance, we studied skin and not muscle microvascular function because, in skin, functional capillary recruitment can be directly visualized and measured in vivo. Comparable insulin-mediated metabolic and microvascular effects can be demonstrated in skin and muscle.[17,29] In addition, skin microvascular function is associated with blood pressure,[8,13] and hypertension is characterized by defects in both muscle and skin microvascular function.[13,30] Thus, the study of skin microvascular function seems a reasonable model of muscle microvascular function.

Caution should be taken in extrapolating the present findings in women to men, although previous data have shown that the association between waist-to-hip ratio and skin microvascular function is similar in men and women (Erik H. Serné, MD, PhD, et al, unpublished data, 2002). We studied women to minimize effects of sex differences. Previous studies have shown sex differences in skin blood flow responses to provocative maneuvers[31] and in endothelial NO production in skin microvasculature.[32] In addition, extrapolation to other populations of women should be performed with caution because of possible selection bias. However, if anything, one would expect that the present results underestimated the effects of obesity in general, because we studied a group of healthy, nonhypertensive, and nondiabetic obese women. Finally, the small number of participants may have concealed an interaction of obesity in the relationship between microvascular function and insulin-mediated glucose uptake.

In summary, we are the first to report that obesity is associated with impaired skin microvascular function, measured as postocclusive capillary recruitment and endothelium-dependent vasodilation, in the basal state and during physiological hyperinsulinemia. In addition, we demonstrated that impaired microvascular function is associated with increased blood pressure and impaired insulin sensitivity in lean and obese women. The obesity-related impairment in microvascular function may contribute to the increased risk of developing microangiopathy, hypertension, and insulin resistance. Further studies are necessary to elucidate the mechanisms that link obesity and impairment of microvascular function. Such studies are an important step to develop strategies in the prevention of obesity-associated microangiopathy, hypertension, and insulin resistance.

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